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ENVIRONMENTAL FACTORS INVOLVED IN THE DEVELOPMENT OF TOLERANCE TO BEHAVIORAL EFFECTS OF DELTA-9-TETRAHYDROCANNABINOL.

Final Progress Report

by

(10) Marc N. Branch, Ph.D

(11) Aug[redacted]76

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Squirrel monkeys were trained under a variety of behavioral procedures, and then Δ^9-tetrahydrocannabinol was administered daily until tolerance developed. The aim of these experiments is to examine the interaction between behavioral procedures and the development of tolerance to behavioral effects of Δ^9-tetrahydrocannabinol. Three classes of experiments were performed. The first group of experiments examined the roles of behavioral "cost" and baseline response rates as determinants (cont'd)

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of tolerance development. Two complementary experiments in which either high or low rates were compared with moderate response rates were conducted. In both cases administration of Δ^9tetrahydrocannabinol resulted in relatively less loss of reinforcement under conditions where moderate rates prevail than where either the high or low rates prevail. Tolerance developed under all procedures and appeared to be unrelated to behavioral cost except in one experiment.

The second experiment dealt with task complexity. The experiment examined the interaction of repeated drug administration with the length of a complex response sequence. Testing with the shortest sequence was completed, and overall rate of output of behavior took longer to recover from repeated drug administration than did accuracy of performance.

The last experiment compared tolerance development across different motivations. Equivalent performances were established under three different motivational sets, and two doses were tested. Tolerance developed under all motivational sets, with no indication of motivation-specific effects.

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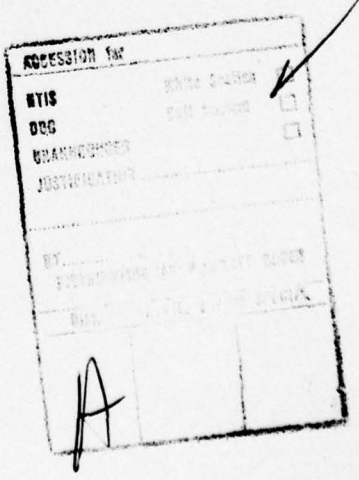

FOREWORD

In conducting the research described in this report, the investigator adhered to the "Guide for Laboratory Animal Facilities and Care", as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Science-National Research Council.

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INTRODUCTION AND BACKGROUND

This project consisted of a series of experiments aimed at determing both quantitative and qualitative aspects of the envirgnment that affect the development of tolerance to behavioral effects of Δ^9-tetrahydrocannabinol (Δ^9-THC), a compound that appears to be the major active consituent of marijuana (Mechoulam et al., 1970). The experiments, conducted with animal subjects, were concerned with variables that determine the degree of tolerance observed, and, in those situations where tolerance does develop, with variables that influence the rate at which the tolerance occurs.

Specifically, three general questions were addressed. One set of experiments was directed at a determination of how schedules of food presentation for simple motor responses act as determinants of the rate at which tolerance to behavioral effects of Δ^9-THC develops. Schedules of food presentation have been shown to be powerful determinants of the degree of tolerance that is observed when amphetamine is administered chronically (Schuster et al., 1966). Two types of experiments were conducted in this part of the project. One type compared the development of tolerance under procedures where the subject's response rate directly determines the frequency of food presentation to the development of tolerance under conditions where the frequency of food delivery is nearly independent of the subject's response rate. The other type of experiment involved procedures in which frequency of food delivery and rate of responding are controlled independently. This allowed an assessment of the role of these two variables.

A second set of experiments attempted to systematically investigate the role of response "complexity" in the development of tolerance to behavioral effects of Δ^9-THC. In these experiments the "difficulty" or "complexity" of a task was systematically varied, and the effects of Δ^9-THC examined. Unfortunately, time did not permit completion of these experiments.

The third set of experiments investigated the role of the type of consequent events that maintains a simple motor response. Behavioral consequences that are considered both positive (e.g., food for a food-deprived animal) and negative (e.g., electric shock) were used to maintain similar rates and temporal patterns of responding, and these baselines used to study the effects of Δ^9-THC.

I. Experiments involving manipulation of type of schedule, and parameters of schedules, of food presentation.

The immediate objective of this group of experiments was to determine how the type of schedule of food presentation, as well as the parameters of such schedules, can modulate the rate at which tolerance develops.

The effects of acute administration of Δ^9-THC on behavior controlled by schedules of food or water presentation have been studied by many investigators (e.g., Black et al., 1970: Boyd et al., 1963; Carlini, 1968; Frankenheim et al., 1971; Ferraro et al., 1971), and the usual finding is that Δ^9-THC reduces response rates under most schedules.

There are, however, reports of rate increases under some schedules (e.g., Ferraro and Grisham, 1972; Conrad et al., 1972; Manning, 1973). Other data also indicate that the acute effects of Δ^9-THC can differ, depending on the schedule of food presentation that maintains the behavior (e.g., Ferraro et al., 1972), and also depending on the behavioral history of the animal (e.g., Drew and Miller, 1973).

Some data also suggest that the rate at which tolerance to Δ^9-THC develops varies under different schedules of food presentation. For example, McMillan et al. (1970) reported that acute administration of 1.8 mg/kg Δ^9-THC to pigeons reduced rates of pecking under a procedure in which, in the presence of one set of stimuli, every 30th peck produced access to food (a fixed-ratio 30 schedule), and in the presence of a second set of stimuli, the first peck after five minutes had passed produced access to food (a fixed-interval 5-min schedule). Under a chronic dosing regimen the key-pecking rates rose to control values, with a suggestion that key pecking under the fixed-ratio schedule recovered more rapidly. In subsequent reports (McMillan et al., 1971, 1972) such a difference was not directly reported by these investigators, but in these reports the data reported are averages for a number of subjects so it is difficult to determine whether the difference is reliably obtained. In a more dramatic demonstration, Harris et al. (1972) showed that whether or not tolerance to the rate-decreasing effects of Δ^9-THC developed at all depended on the schedule of food presentation in effect. These investigators employed rhesus monkeys in a task where presses on a lever produced food according to either a fixed-ratio 30-response schedule, or according to a schedule that required that presses be spaced by a least 15 seconds. Each schedule was correlated with a distinctive stimulus. Lever pressing under the schedule that required spaced responding showed tolerance to Δ^9-THC whereas pressing under the fixed-ratio schedule did not. These experiments show that the rate at which tolerance develops to the behavioral effects of Δ^9-THC can depend on the schedule of food presentation that maintains a simple manipulative response.

In the present project two complementary experiments examined the role of control of frequency of food presentation by an animal as a determinant of tolerance development. In the first experiment the effects of chronic administration of Δ^9-THC on behavior maintained by a schedule that produces a high response rate and also allows the animal to directly control the frequency of food delivery was compared to the effects of chronic administration on behavior under a schedule that controls a lower rate but which has an identical frequency of food presentation. Specifically, behavior under a schedule according to which food is presented dependent on a variable number of responses being emitted (a variable-ratio schedule) is compared to behavior under a schedule that provides the same temporal distribution of food presentation but which doesn't require a specified number of responses for each food delivery (a variable-interval schedule). When the temporal distribution of food presentation is equal under variable-interval and variable-ratio schedules, the rate of responding is usually higher under the variable-ratio schedule (Ferster and Skinner, 1975; Zuriff, 1970).

In the second experiment, the schedule that allowed the animal to control the frequency of food delivery was also a schedule that produces a

low response rate. Specifically, a procedure where delivery of food depends on the animal spacing its responses (a differential-reinforcement-of-low-rate, or DRL, schedule) was alternated with a procedure in which the temporal distribution of food presentation was about the same as that under the DRL schedule, but no spacing of responses was required (a variable-interval schedule). In this experiment the schedule that allowed the animal to directly control the frequency of food delivery produced a much lower rate than the schedule under which the frequency of food delivery was more independent.

A tentative hypothesis about the final outcome of these two experiments that is consistent with the literature was that tolerance should develop most rapidly under procedures where a low rate prevailed and where the animal had a high degree of control over the frequency of food delivery. Conversely, tolerance should develop most slowly under conditions where a high rate prevails, and the animal has relatively little control over the frequency and distribution of food presentation.

This proposed interaction of rate of responding and degree of control by the animal over the frequency of food delivery was examined further in another experiment. In this experiment, procedures that allowed response rate to be controlled independently of frequency of food delivery were employed. Three different response rates, high, medium, and low, were generated, all of which led to the same frequency of food presentation. The rates were engendered using procedures similar to those employed by Blackman (1968), and each rate occurred in the presence of a specific stimulus. The effects of chronic administration of Δ^9-THC on these behaviors allowed direct assessment of the influence of baseline response rate on the development of tolerance to the behavioral effects of Δ^9-THC. This procedure also led to differential reductions in frequency of food presentation as a function of drug administration. This experiment, then, also allowed a test of the importance of degree of reduction in frequency of food presentation as a determinant of tolerance to Δ^9-THC.

II. Response "difficulty" as a determinant of tolerance to behavioral effects of Δ^9-THC.

Although tolerance seems a relatively reliable outcome when simple motor responses are maintained by schedules of positive reinforcement (e.g., Carlini, 1968; Ferraro and Grisham, 1972; McMillan et al., 1970; McMillan et al., 1972; cf., however, Snyder et al., 1975), it has been reported that tolerance does not develop as readily when more "complex" tasks are used. Ferraro and Grilly (1973) recently reported a failure to observe tolerance to the accuracy-reducing effects of Δ^9-THC in a delayed-matching task. In this experiment chimpanzees could produce food by identifying a stimulus that matched one shown 20 seconds previously. Repeated administration, for 42 consecutive days, of a dose of Δ^9-THC that reduced accuracy did not result in tolerance development. In a more recent report (Ferraro and Grilly, 1974), Ferraro and his colleagues have shown that some tolerance is eventually observed under this procedure. A related finding was presented by Elsmore (1972) who trained monkeys in a two-choice discrimination task. Elsmore's monkeys initiated trials in which either the duration of a light (Experiment I) or the frequency

of clicks (Experiment II) served as the discriminative stimulus for pressing one of two levers. He reported that tolerance to the suppressive effects of Δ^9-THC on rate of trial initiation developed more rapidly than did tolerance to the accuracy-reducing effects of the drug. These two experiments show that the type of behavioral measure employed (i.e., a rate measure versus an accuracy measure) can determine the degeee of tolerance observed, and also suggest that task difficulty might be a factor determining whether tolerance is observed.

An experiment was conducted to determine if task "difficulty" (i.e., the degree to which responding can be brought under stimulus control) modulates the rate at which tolerance develops. The experiment examined how the required length of a sequence affects tolerance development. Briefly summarized, this experiment involved extending a behavioral sequence (in steps) from two to five responses and determining the rate at which tolerance develops for each level of complexity. Time did not permit completion of this experiment so only data from experiments where the sequence was two responses long are reported.

III. Role of the type of event maintaining behavior in the development of tolerance to the behavioral effects of Δ^9-THC.

Although it has been persuasively argued that the acute effects of many pharmacologic agents on behavior depend more on the rate and temporal pattern of responding than on the event maintaining the behavior (Kelleher and Morse, 1968), recent data (McKearney, 1974) show that when patterns and rates of lever pressing by squirrel monkeys are similar under schedules of shock presentation and under schedules of food presentation, differential effects of both morphine and chlorpromazine are observed. Given these kinds of differential acute effects there is a strong possibility that differential effects will be obtained under chronic regimens.

As mentioned above, the literature on the development of tolerance to the behavioral effects of Δ^9-THC contains many instances of tolerance observed when simple responses are maintained by schedules of positive reinforcement. On the other hand, when procedures that employ "unlearned" (elicited) behavior are used, and when procedures in which behavior is maintained by avoidance of electric shock are used, it is often the case that tolerance is not observed (e.g., Orsinger and Fulginiti, 1970; Barry and Kubena, 1971), although there are sometimes clear cases of tolerance when avoidance behavior is tested (e.g., Manning, 1975).

In the present project an experiment was performed in which similar rates and temporal patterns of lever pressing maintained by three different types of events; food presentation, termination of a stimulus associated with the periodic delivery of electric shock (cf. Kelleher and Morse, 1964), and presentation of electric shock (cf. McKearney, 1968). The maintenance of responding by termination of a stimulus associated with the periodic delivery of shock (a shock-stimulus complex) can be classified as an avoidance procedure (Kelleher and Morse, 1964), and some have suggested that responding maintained by electric shock presentation (schedules of response-produced shock) is in some sense elicited (Hutchinson et al., 1971). A tentative hypothesis, then, regarding the outcome of chronic

administration of Δ^9-THC, was that tolerance would develop most rapidly under the schedule of food presentation, less rapidly under the schedule of termination of a shock-stimulus complex, and least rapidly, or perhaps not at all, under the schedule of shock presentation.

IV. Determination of the time course of action of THC.

A final experiment was conducted to obtain basic information regarding the duration of action of THC in the squirrel monkey when THC is administered intramuscularly. Early in the series of experiments reported here we discovered that the oral route of administration was not a reliable one for squirrel monkeys. Oral administration was often followed by vomiting which necessarily resulted in less than adequate control of dose. In addition it was recently reported that THC is not absorbed well from the gut of squirrel monkeys (Würsh et al., 1972). In our experiments, monkeys were a administered the drug 15 min, 30 min, 60 min, or 150 min before a session during which a variable-interval schedule of food presentation was in effect. Three doses were tested, so changes in the dose-effect curves could be examined as a function of time since injection.

GENERAL METHODS

Squirrel monkeys (Saimiri Sciureus) were used in all procedures. All animals were maintained at 85% of their free-feeding weights, and housed in individual cages. The monkeys had free access to vitamin-enriched water while in their home cages.

During experiments the squirrel monkeys worked in restraining chairs that were housed in sound-attenuating enclusures. The restraining chairs were equipped with levers, response keys, feeders, tail stocks and stimulus lights as needed. Sessions were monitored and controlled by a PDP-8 computer utilizing the SKED process-control system.

The Δ^9-THC in these experiments was suspended in a 10% (v/v) solution of Tween 80 in 0.9% sodium chloride solution. The drug was administered intramuscularly, in a volume of 0.25 mg/kg body weight, one hour prior to a session. The long pretreatment time was used since earlier reports of experiments with squirrel monkeys (Scheckel et al., 1968) show a very slow onset of action of Δ^9-THC. Administrations of the vehicle alone were also examined.

In order to enhance the comparability of the data from the wide range of experiments outlined here, chronic regimens were the same under all sets of behavioral parameters. Specifically, Δ^9-THC was given once per day for twenty consecutive days, or until the behavior examined returned to control levels.

In those experiments in which food was used to maintain responding, monkeys were able to produce 190-mg banana-flavored food pellets. Sessions were conducted daily, seven days a week, and sessions generally lasted from 40 to 90 minutes, depending on the procedure.

In many of the experiments multiple schedules (Ferster and Skinner, 1957) were used. Multiple schedules consist of at least two schedules of reinforcement, and each schedule is associated with a different stimulus. The use of multiple schedules allows investigation of more than one schedule at a time in a single animal.

The Δ^1-THC was stored in refrigerated darkness, and was safeguarded according to guidelines suggested by the Bureau of Narcotics and Dangerous Drugs in accord with the Comprehensive Drug Abuse Prevention and Control Act of 1970. The principal investigator is licensed by the Drug Enforcement Agency (License No. PB0108820) to obtain and use Δ^1-THC.

SPECIFIC EXPERIMENTS

I. TIME COURSE DETERMINATION

a.) Effects of varying the time between intramuscular injection of Δ^1-THC and the beginning of a test session under a variable-interval schedule of food presentation.

Two monkeys were trained to press a lever under a variable-interval 60-sec schedule of food presentation. Sessions lasted until either 40 food pellets had been delivered or until 50 min had elapsed, whichever came first. Presession injection times of 15 min, 30 min, 60 min and 90 min were examined. Dosages of 0.25, 0.50 and 1.00 mg/kg were tested at each of the presession injection times. The variable-interval schedule produced constant, moderate rates of lever pressing in both monkeys. Monkey 514's rate remained constant throughout the experiment, whereas Monkey 521's baseline shifted dramatically about half way through the experiments. Sessions prior to those in which THC was administered were designated as control sessions, and the mean rate for Monkey 514 during control sessions (± S.D.) was 45.7 (3.6) the two different control rates for Monkey 521 (±S.D.) were 32.9(5.5) and 73.1(9.0).THC was not administered to Monkey 521 while its baseline rate was shifting from the lower rate to the higher one, thus there was about a 40-day period during which drugs were not administered to this monkey. At least 7 days elapsed between successive administrations of THC. Figure 1 shows dose-effect curves for both Monkeys under each of the four presession injection times. There was no systematic relationship between presession injection time and shape or location of the dose effect curve. The 1.0-mg/kg dosage was also injected 150 min prior to a session with the result that response rate was suppressed to a level comparable to that seen with other presession injection times. Taken in sum, the results show that the effect of a given dosage of THC began in about 15 min and lasted at least 190 min.

II. MODULATION OF THE DEVELOPMENT OF TOLERANCE TO BEHAVIORAL EFFECTS OF THC BY RATE OF RESPONDING AND FREQUENCY OF FOOD PRESENTATION.

a.) Development of tolerance under a multiple schedule in which high rates of responding are associated with equal frequencies of food presentation, but are not equally correlated with the frequency of food presentation.

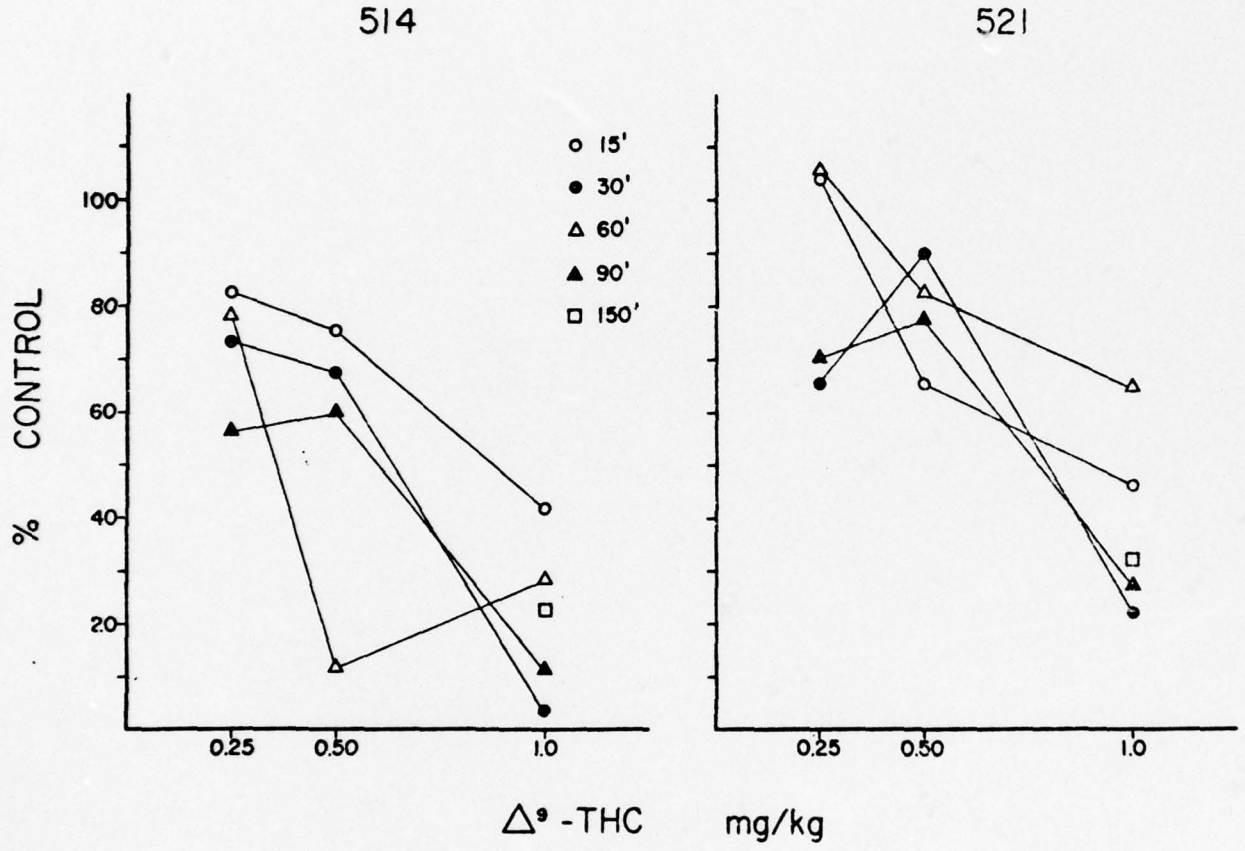

Fig. 1. Percent of control response rate as a function of dose of THC for Monkeys 514 and 521. The different symbols indicate different presession injection times.

The monkeys were trained on a procedure where lever presses produced food pellets according to a schedule under which the delivery of food depends on the number of presses, and the number of presses required varies for each pellet presentation (a variable-ratio schedule). This schedule engendered high, constant response rates. When lever pressing was well established under this schedule, which allowed the animal to directly control the temporal frequency of food delivery, a multiple schedule was instituted. In the presence of one stimulus (white pilot lights) a variable-ratio 74 schedule was in effect. In the presence of a second stimulus (blue pilot lights) a schedule is put into effect that allowed lever presses to produce food pellets with approximately the same frequency and distribution as during the variable-ratio schedule, but that required that only a single response be made after the schedule had arranged that a pellet was available (a variable-interval schedule). This schedule produced moderate rates of responding. Figure 2 shows cumulative response records from the two monkeys that served in this experiment. Each schedule and its associated stimulus (i.e., each component of the multiple schedule) was in effect for alternate five-minute periods throughout a session. The intervals in the variable-interval schedule were determined by using the inter-pellet intervals observed during the variable-ratio schedule. That is, the times between pellet deliveries under the variable-ratio schedule were recorded, and a variable-interval schedule that was comprised of the average of these inter-pellet intervals is employed. Thus, the variable-interval schedule was "yoked" to the variable-ratio schedule. A new variable-interval schedule was constructed every seven to fourteen sessions until performance under the variable-ratio schedule was stable enough so that there were negligible changes in the variable-interval schedule.

Monkey 509 was the first to receive Δ^9-THC. He received 1.0 mg/kg of the drug for 20 consecutive sessions, followed by 53 days without drug. After the 53-day period, the same dose was again administered for 20 consecutive days to see if the original effects could be reproduced. After 315 days, 0.25 mg/kg Δ^9-THC was administered for 20 days to examine the effects of a lower dosage.

A cumulative response record from the first session under 1.0 mg/kg Δ^9-THC is shown in Figure 3. The drug produced an overall decrease in response rate in both components. The decrease was roughly uniform throughout the session. Figure 4 displays quantitative data from both the chronic series of administration in which 1.0 mg/kg was administered. The figure shows that prior to both series an approximately equal number of pellets was being earned in each schedule, and that the response rate during the variable-ratio schedule was consistently higher than the rate during the variable-interval schedule. Over the course of both 20-day series of drug administration, tolerance developed to the depressive effects of the drug in both components of the multiple schedule, and tolerance appeared to develop at the same rate under both schedules. Also of interest is the fact that during drug sessions there were no consistent differences in response rates between the two components. When administration of the drug was discontinued (injections of the vehicle continued) after the first 20-day phase of chronic administration, response rates gradually decreased for about 10 sessions and then increased toward control levels. Control levels of responding were recaptured 30 days after the last dose of Δ^9-THC. When drug administrations were halted after the second 20-day chronic series, rates immediately dropped, and did not return to baseline until much later. Figure 4 shows data from the

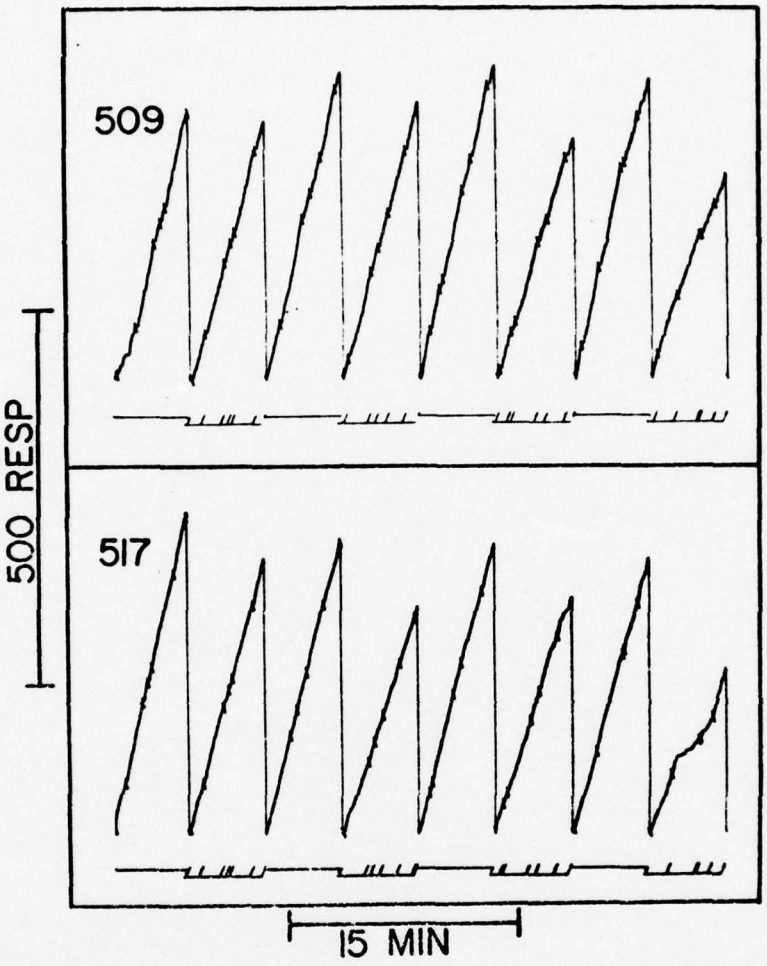

Fig. 2. Cumulative response records from Monkeys 509 and 517 under the multiple variable-ratio (event pen up) variable-interval (event pen down) schedule. Y axis: cumulative lever presses. X-axis: time. The pen reset to the baseline at the end of each component. Short diagonal marks indicate food-pellet delivery. The marks on the event line during variable-interval components also indicate food delivery.

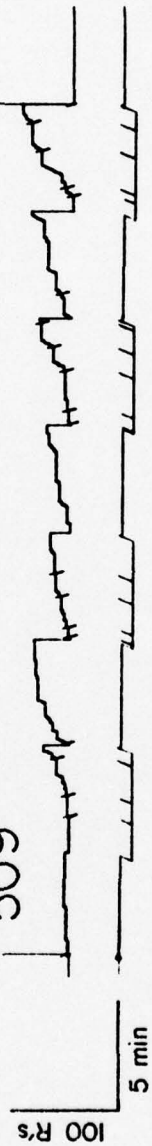

Fig. 3. Cumulative response record from Monkey 509 following injection of 1.0 mg/kg of THC. Details as in Fig. 2.

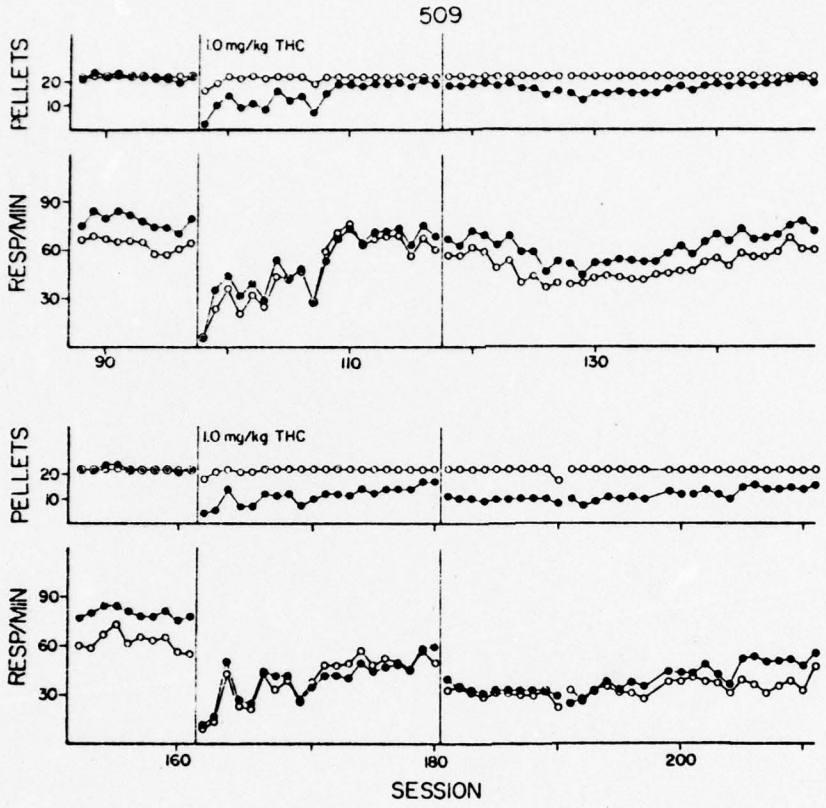

Fig. 4. Mean response rates of Monkey 509 and number of pellets delivered in each component of the multiple schedule before, during, and after daily administration of 1.0 mg/kg of THC. Open circles show data from the variable-interval component. Filled circles show data from the variable ratio component. Injections of the vehicle occurred on the 10 days following cessation of daily injections of THC.

sessions before which Monkey 509 was administered 0.25 mg/kg of Δ^9-THC. As previously, the initial effect of the drug was to reduce rate under the variable-ratio. However, the reduction was not a severe as with 1.0 mkg/kg, and the variable-interval rate was not appreciably suppressed. Differential responding was maintained throughout the chronic dosing sequence. Tolerance to the rate-decreasing effects of Δ^9-THC during the variable-ratio schedule developed in 9 sessions. Unfortunately, an apparatus failure (feeder jam) occurred on the day drugging was discontinued, rendering those data uninterpretable.

Monkey 517 was also exposed to 20 days of daily administration of 1.0 mg/kg of Δ^9-THC. Data from this monkey are shown in Figure 6. At the end of the phase it was discovered that Monkey 517 had a severely abcessed molar, so it is not possible to tell whether the decline in rates observed during the last 12 sessions of drug administration were due to the drug or to the abcess. Over the first 10 sessions, however, it appeared that tolerance was developing at equal rates in both components.

Two other monkeys were also trained under this procedure, but the contract expired before either could be administered drugs.

b.) Development of tolerance under a multiple schedule in which low and moderate rates are associated with equal frequencies of food delivery.

The animals were first trained to respond (press a lever) under a schedule where presentation of food depended on responses being spaced by some minimum amount of time (a differential-reinforcement-of-low-rate, or DRL, schedule). THis schedule resulted in a low rate, and a significant proportion of the interresponse times (times between two lever presses) were slightly longer than the minimum (28 sec) required for food presentation. When behavior stabilized under this procedure, a multiple schedule was put into effect. One component of the multiple schedule is the DRL schedule, and the other component is a variable-interval schedule, and the components alternate every 5 minutes. The variable interval schedule was constructed with a distribution of intervals that approximates the distribution of interpellet times during the previous DRL component. Specifically, a response could not produce a pellet for the first 28 sec following delivery of the previous pellet. Following this 28 sec period a probability generator is tested once each second and assigns pellet availability. The probability of assignment has been adjusted to keep overall frequency of food delivery roughly equal in both components of the multiple schedule. The two components of the multiple schedule controlled quite different performances. Figure 7 shows cumulative response records of pressing by the two monkeys currently in the experiment. The variable-interval schedule controlled a rate of pressing from five to ten times higher than the rate controlled by the DRL schedule. The DRL schedule also exerted control over the spacing of lever presses while it was in effect.

Both monkeys were exposed to chronic administration of 0.25 mg/kg and then to chronic administration of 1.0 mg/kg. The number of days that elapsed between the end of one series of administrations and the beginning

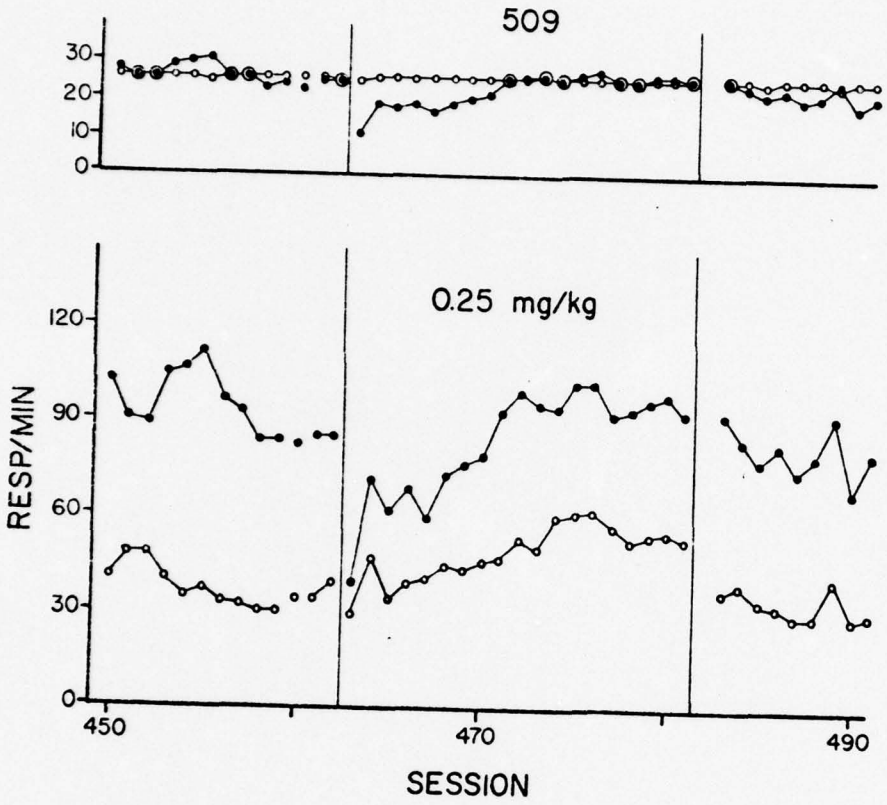

Fig. 5. Mean response rates of Monkey 509 and number of pellets delivered in each component of the multiple schedule before during and after daily administration of 0.25 mg/kg of THC. Open points are data from the variable-interval components. Filled circles are data from the variable-ratio schedule. The vehicle was administered prior to session 460 and sessions 483-491.

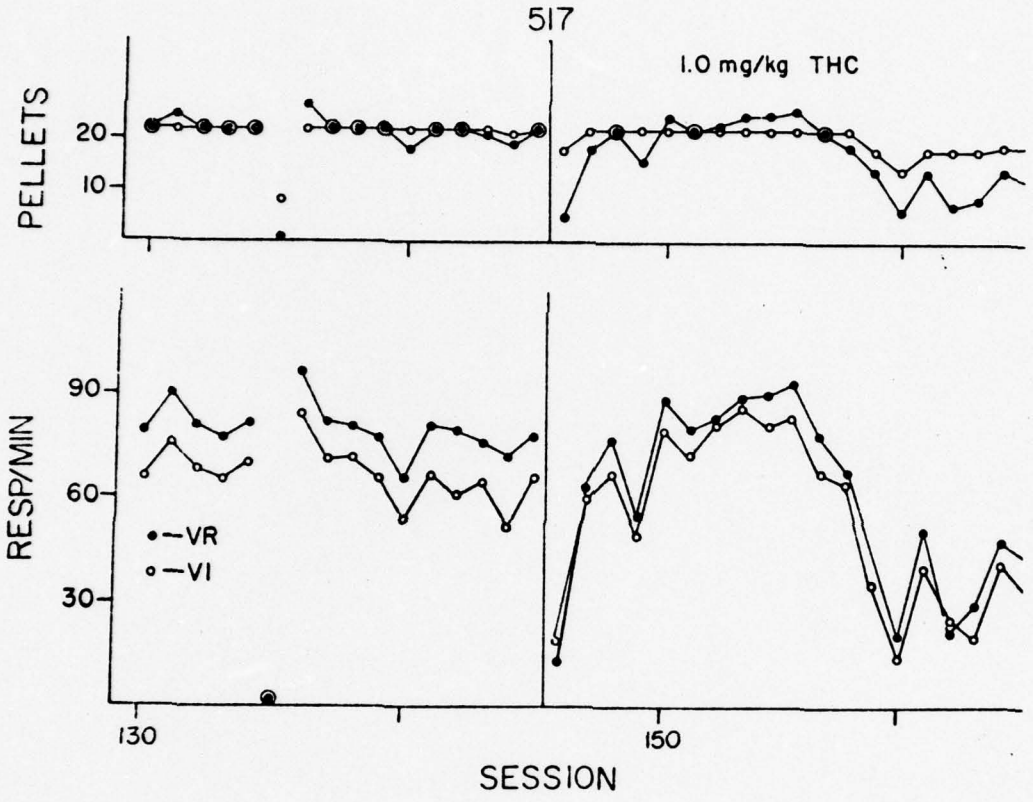

Fig. 6. Mean response rates of Monkey 517 and number of pellets delivered in each component of the multiple schedule before and during daily administration of 1.0 mg/kg of THC. 1.0 mg/kg of THC was also administered prior to session 135. Points have the same meaning as those in Figs. 4 and 5.

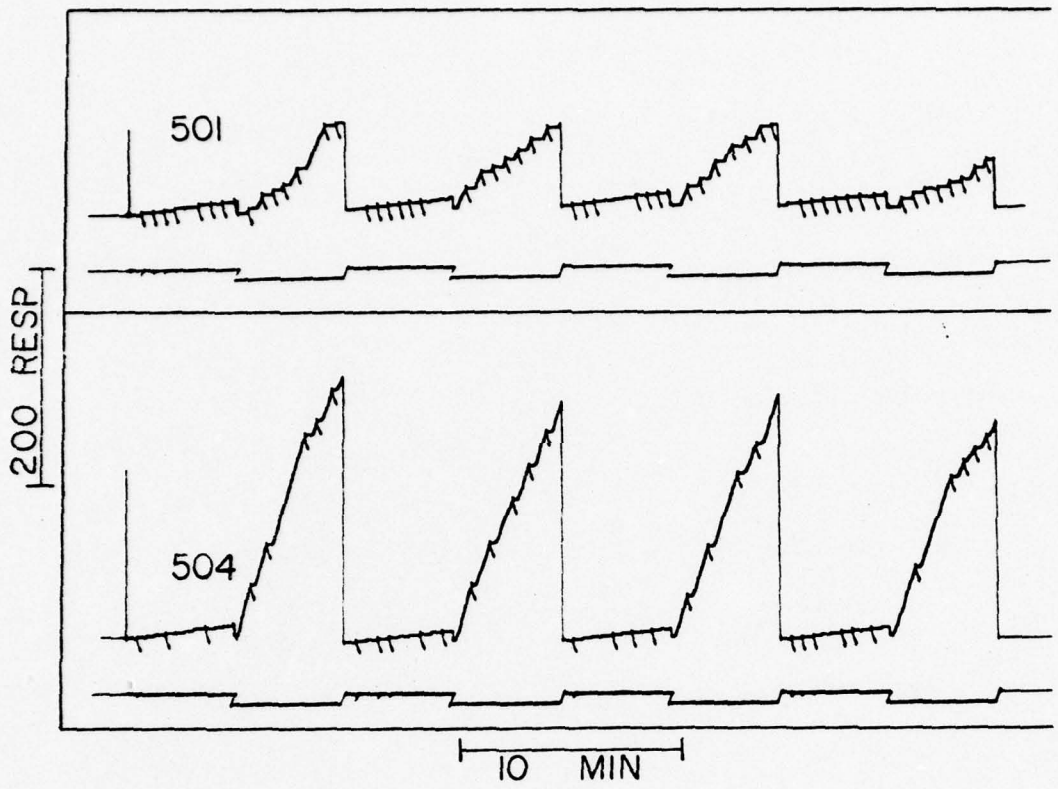

Fig. 7. Cumulative response racords from Monkeys 501 and 504 under a multiple DRL variable-interval schedule. Y-axis: Cumulative lever presses X-axis: time. The event pen was deflected downward during variable-interval components and the stepping pen reset to baseline at the end of each component. Short diagonal marks indicate delivery of a food pellet.

of the next was 274 for Monkey 501 and 176 for 504. Figures 8 and 9 show overall response rate data from both series for Monkey 501. Both doses initially eliminated lever pressing. Upon subsequent administrations, rates during both the DRL and variable-interval schedules were increased above baseline. Further administrations resulted in no change in the variable-interval rate and a slight tendency for rate in the DRL component to decline. Upon withdrawal of the drug, both rates dropped; the DRL rate to near baseline, the VI rate to below baseline. The VI rate returned to baseline levels after about 5 sessions following discontinuation of administration of 0.25 mg/kg and after about 20 sessions following the 1.0-mg/kg series. Figures 10 and 11 show interresponse time (IRT) distributions for selected sessions before, during, and after the drugs were administered. The first session in which responding occurred after initiation of a chronic series was characterized by a dramatic shift of the distribution toward shorter values. By the end of the series, however, the distribution had shifted back towards the longer values. In the first session after the chronic series, very long IRT's tended to occur more frequently.

Figures 12 and 13 show response rate data for Monkey 504. Neither dose of THC eliminated lever pressing by this monkey, however, VI rates were initially greatly suppressed. During the course of administration of 0.25 mg/kg, the VI rate quickly recovered and then exceeded the baseline. During the 1.0-mg/kg series the VI rate rose more slowly, only reaching baseline level after 11 sessions and then never exceeding it. As was the case with Monkey 501, Monkey 504's VI rates dropped sharply when drug administrations were discontinued, and it took longer for the rate to return to baseline following the 1.0 mg/kg series (48 days) than following the 0.25 mg/kg series (10 days) Figures 14 and 15 show IRT data for Monkey 504, and the pattern of effects is similar to that shown by Monkey 501.

Two other Monkeys were trained under this procedure, but the contract expired before any drugs were administered.

c.) Tolerance development under a multiple schedule in which unequal response rates are associated with equal frequencies of response-dependent food presentation.

The monkeys which serve in these experiments were trained to press a lever under a multiple schedule that had three components. Each component was associated with a variable-interval schedule with a mean value of 90 sec. In one component, signalled by one color (white), food pellets were delivered according to the variable-interval schedule only following three interresponse times (i.e., times between two presses, IRT) of less than 0.50 sec. Specifically, when the variable-interval schedule arranged that a food pellet was available, the third interresponse time of less than 0.50 sec resulted in the delivery of the pellet and resumption of timing by the variable-interval schedule. The response rate was highest in this component. In the second component, signalled by green light, pellets were delivered according to the variable-interval schedule only following interresponse times between 0.5 and 1.5 sec, and this arrangement produced a moderate rate of responding. In the third component, food was presented according to the variable-interval schedule only after interresponse times longer than 8 sec, and a low rate prevailed during this component. Components lasted 30 minutes each and were presented once each session. Figure 16 shows cumulative response records from both monkeys. The procedure resulted in three distinctly different response rates. Figures 17 and 18

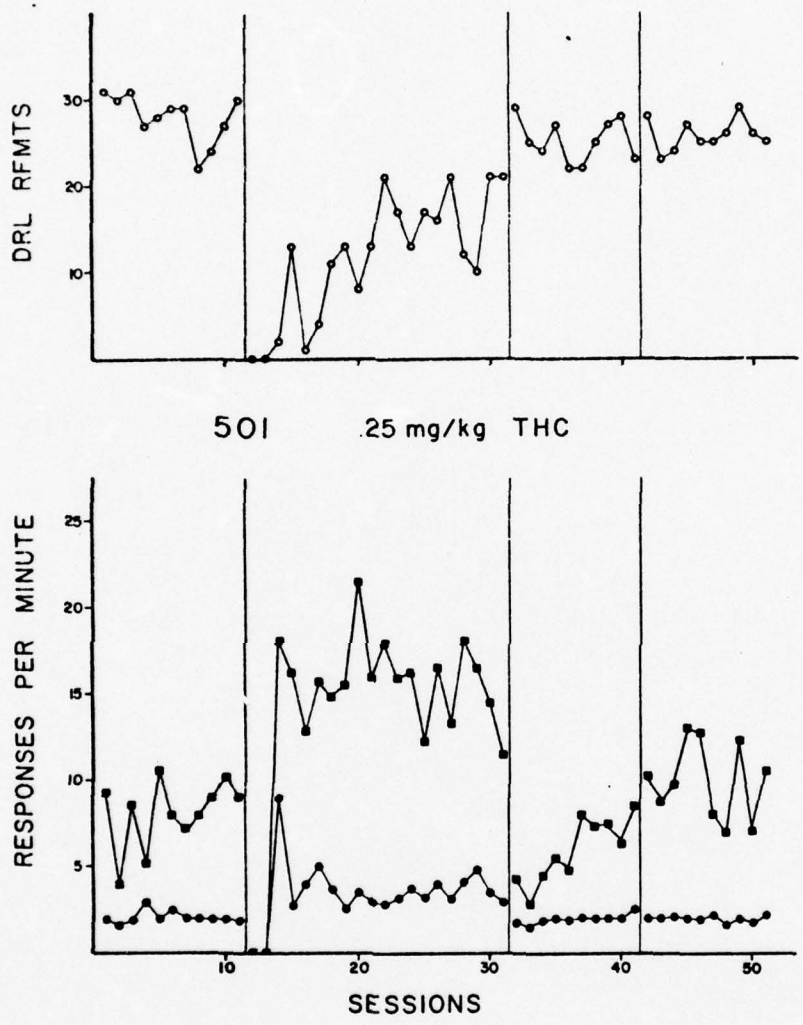

Fig. 8. Response rates before, during and after daily injections of 0.25 mg/kg THC for Monkey 501. The top graph shows the number of food pellets delivered each session under the DRL 28-sec schedule. In the lower graph squares indicate rates in the VI component and circles indicate rates in the DRL component of the multiple schedule. No injections were made over the first eleven sessions. THC was injected prior to the next 20 sessions, and the vehicle prior to the following ten sessions.

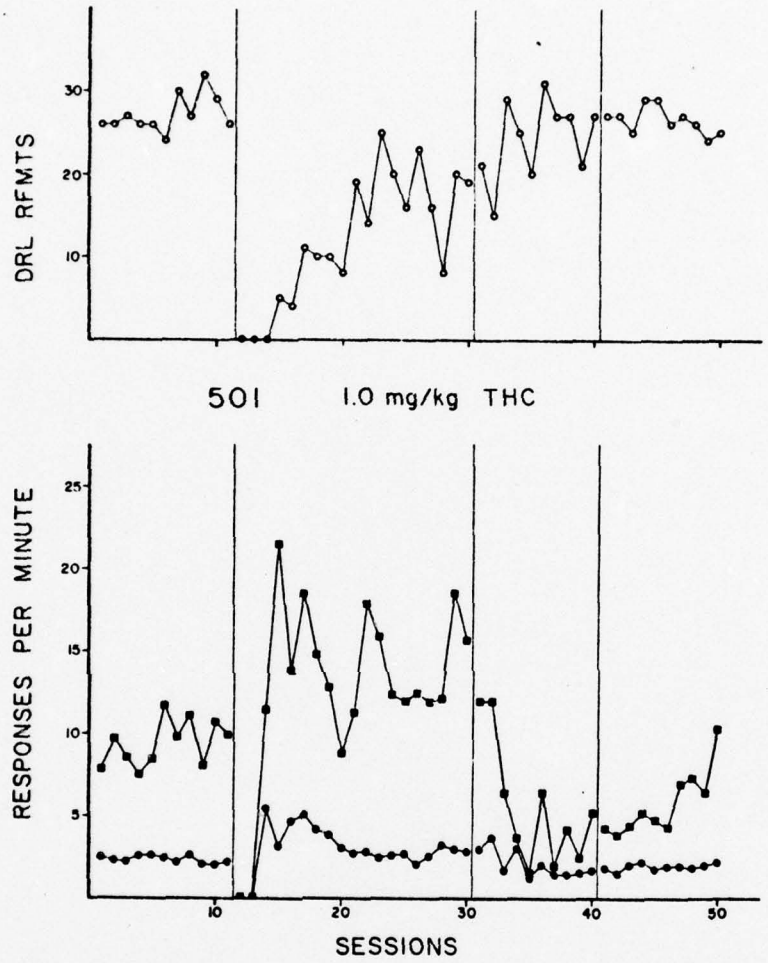

Fig. 9. Response rates before, furing and after daily injections of 1.0 mg/kg THC to Monkey 501. See Fig. 8 for explanation.

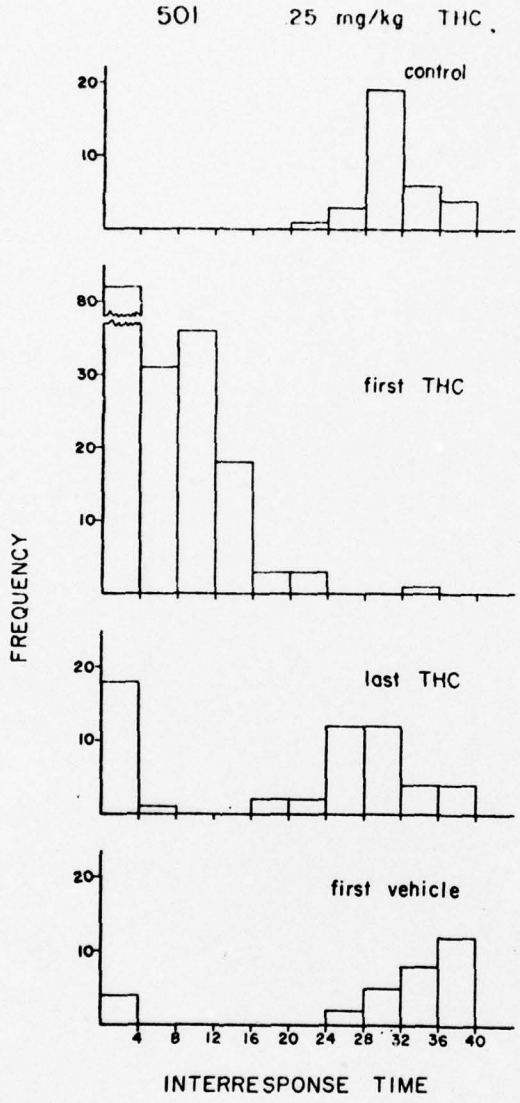

Fig. 10. Interresponse time distributions from Monkey 501. The top graph shows the distribution from the last control session before 0.25 mg/kg injections were begun. The second graph shows data from the third session during chronic administration. The third graph is from the last session in the chronic series. The bottom graph is from the first session following the chronic series.

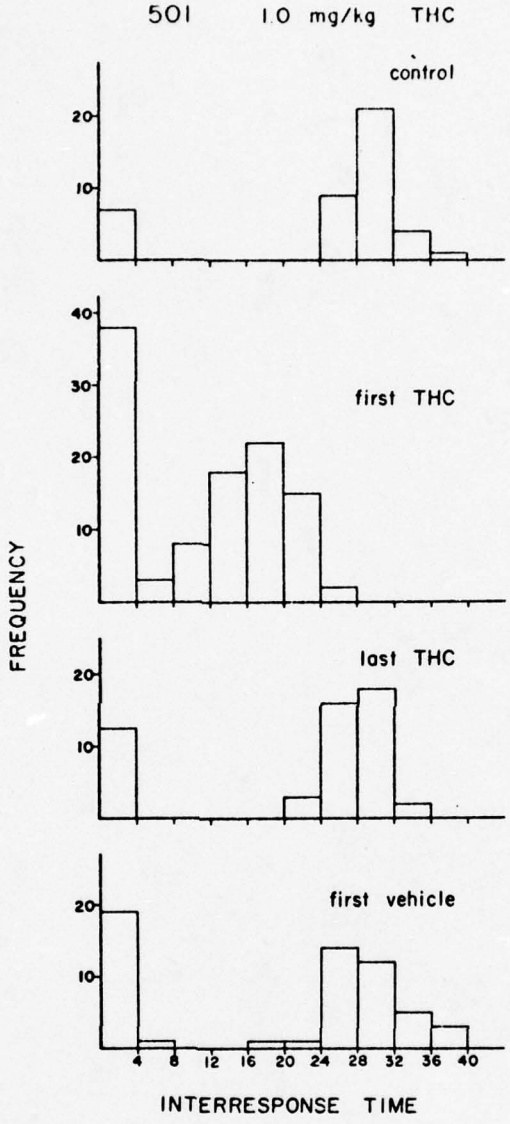

Fig. 11. Interresponse time distributions from Monkey 501 from before during and after daily administration of 1.0 mg/kg THC. See Fig. 10 for explanation.

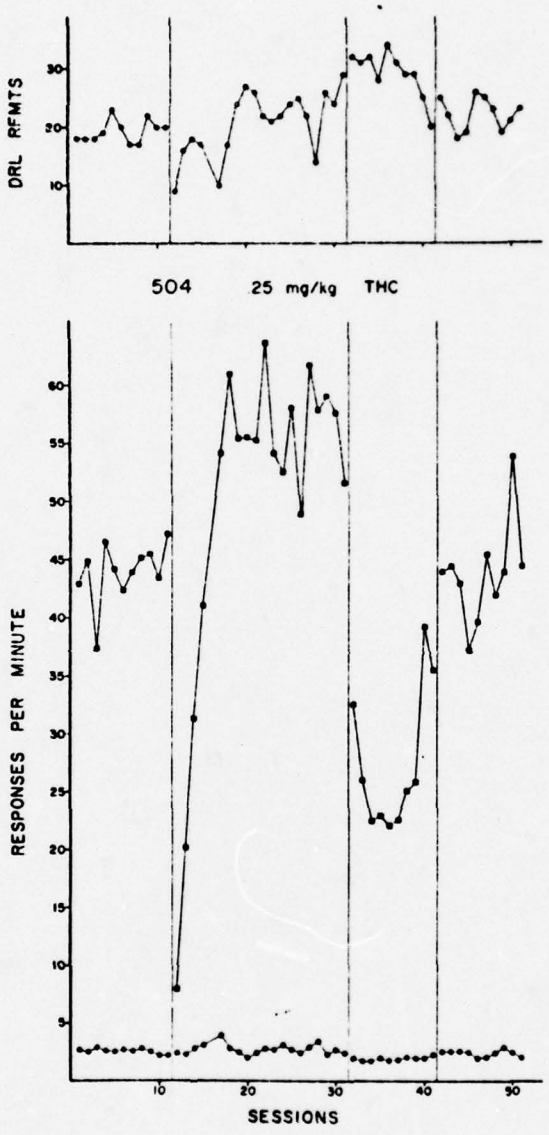

Fig. 12. Response rates for Monkey 504 from sessions before, during and after daily injection of 0.25 mg/kg THC. The vertical lines show changes from no drug to drug, from drug to vehicle, and from vehicle to no drug. See Fig. 8 for further explanation.

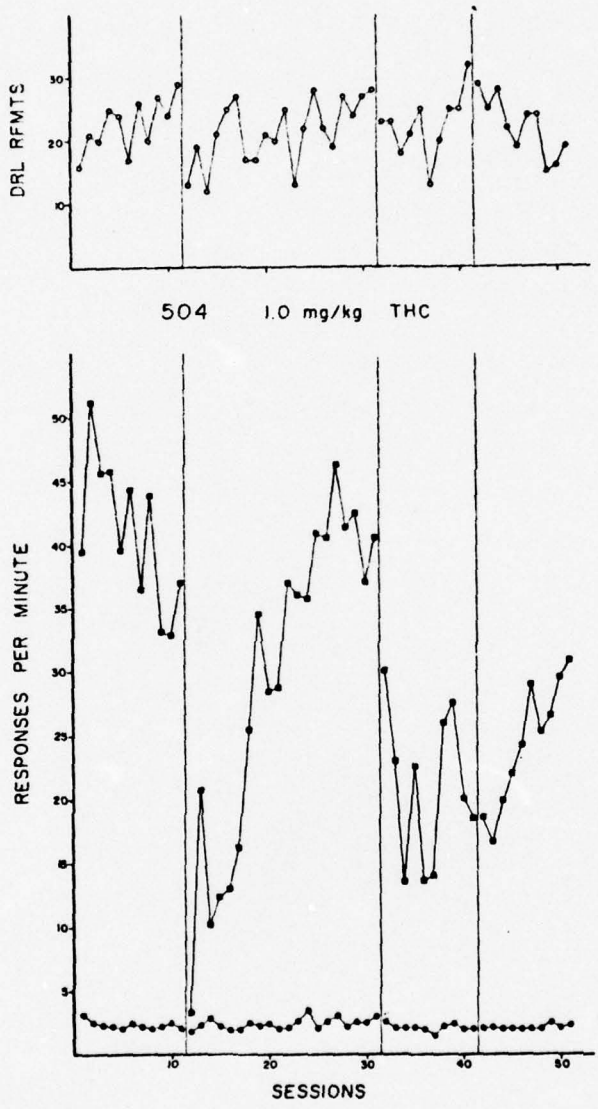

Fig. 13. Response rates for Monkey 504 from sessions before, during and after daily injection of 1.0 mg/kg THC. The figure is constructed as was Fig. 12.

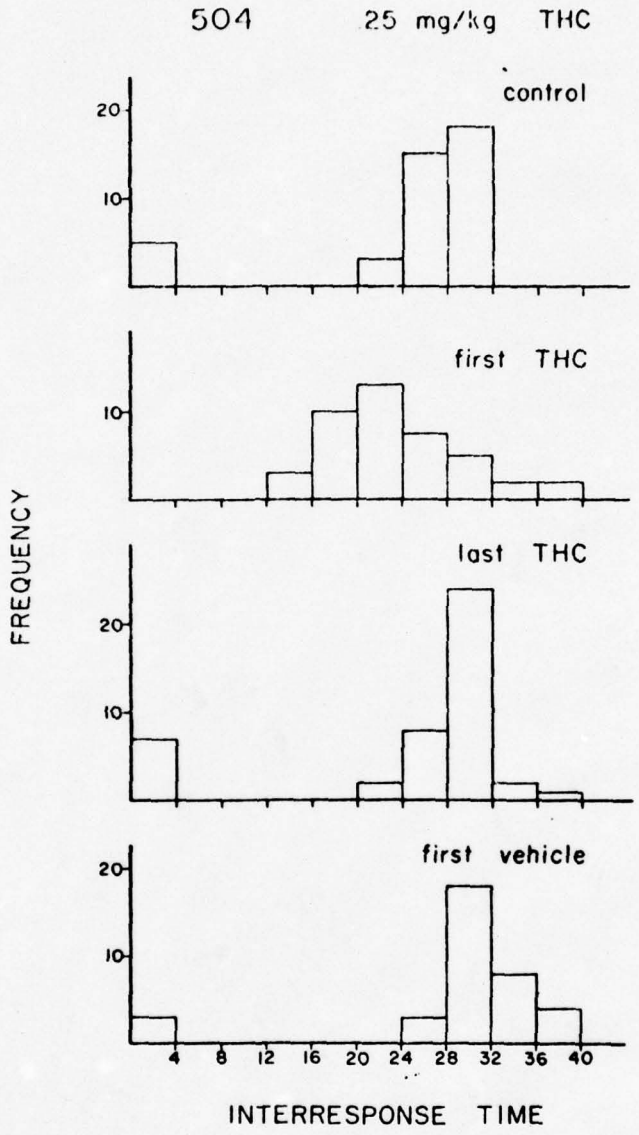

Fig. 14. Interresponse time distributions from a control session, the first session prior to which 0.25 mg/kg THC was administered, the last session of the chronic drug series, and the first session after the chronic series for Monkey 504.

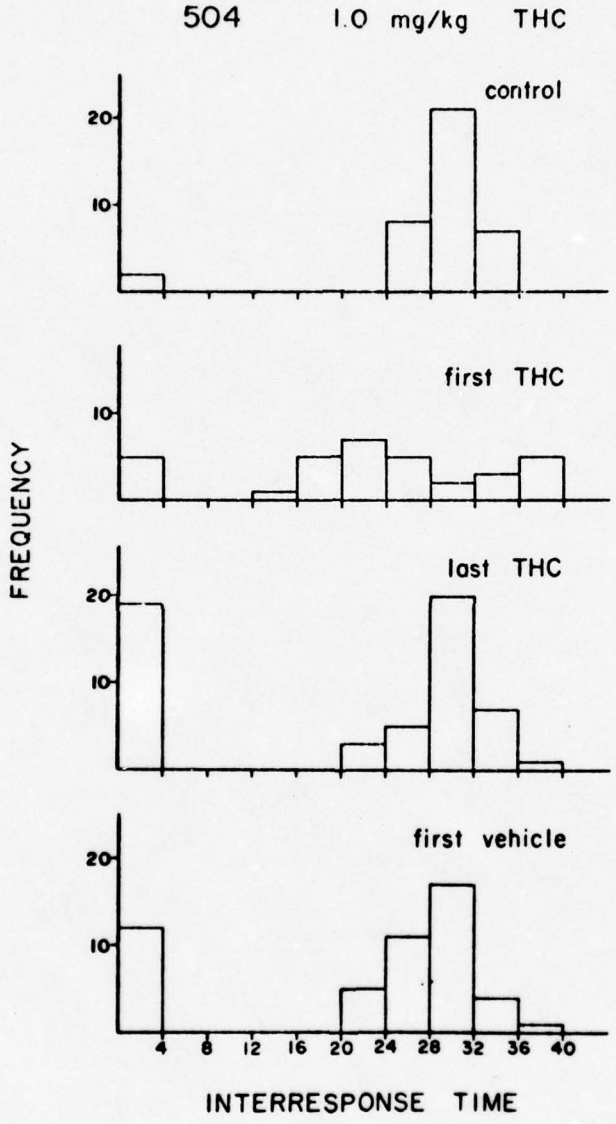

Fig. 15. Interresponse time distributions from before, during and after daily administration of 1.0 mg/kg THC to Monkey 504.

show response-rate and pellet-frequency data before, during and after a series of daily injections of 1.0 mg/kg THC for Monkeys 505 and 513, respectively. Monkey 505's lever pressing was completely suppressed during the first session of drug administration. In subsequent sessions responding was reestablished in all three components. Responding in the component that controlled the low rate was elevated above baseline throughout all sessions of the chronic series, but did reveal a tendency to decrease over the 51 sessions of drug administration. Note, however, that reinforcement frequency had recovered to baseline level within three sessions. Responding during the component that controlled the middle rate returned to baseline in seven sessions, whereas responding in the component that controlled the high rate not only returned to baseline in about the same number of sessions, but exceeded the baseline by the end of the series. Withdrawal of the drug had profound effects. Rates in the components that controlled the middle and high rates were severely depressed and did not recover to baseline levels until about 30 days had passed. Figure 18 shows data from Monkey 513. The pattern of effects is similar to that observed for Monkey 505 except that reinforcement frequency in the component that controlled the low rate was depressed for about 26 sessions before returning to baseline levels. Withdrawal of the drug again resulted in a depression of rate in the components controlling the high and middle rates, and it took about 30 sessions for the baseline to recover.

After 57 sessions had elapsed since the chronic series, dose-effect curves were determined for Monkey 513. The curves are shown in Figure 19. Recall that 1.0 mg/kg had initially suppressed lever pressing. Considerable tolerance existed two months after the chronic series. It took 36 sessions to determine the dose effect curve. The unconnected points above 1.0 mg/kg in Figure 19 show data obtained 153 days after the chronic series. At this point in time 1.0 mg/kg severely suppressed lever pressing but did not completely suppress it as it had originally.

The data from Monkey 505 must be interpreted with caution because this monkey had been exposed to an abortive chronic series of administrations of 1.0 mg/kg. The first chronic series was complicated by the fact that the monkey developed a tooth abcess after 18 sessions and was not exposed to the experimental arrangement for 19 days. THC was administered for these 19 days, however, and also prior to sessions during the subsequent 40 days. The data shown in Figure 17 were collected after 319 days had elapsed since the end of the abortive chronic series. The comparability of effects in Figures 17 and 18 suggest that the data for Monkey 505 are not unrepresentative.

II. DEPENDENCE OF TOLERANCE TO THE BEHAVIORAL EFFECTS OF Δ^9-THC ON THE "COMPLEXITY" OF THE RESPONSE REQUIREMENT.

a.) Length of a response sequence as a determinant of tolerance to the disruptive effects of Δ^9-THC.

The restraining chair for this experiment was equipped with a retractable lever, five response keys that could be illuminated from behind, and a pellet dispenser. The monkeys initiated a trial by making five responses on the

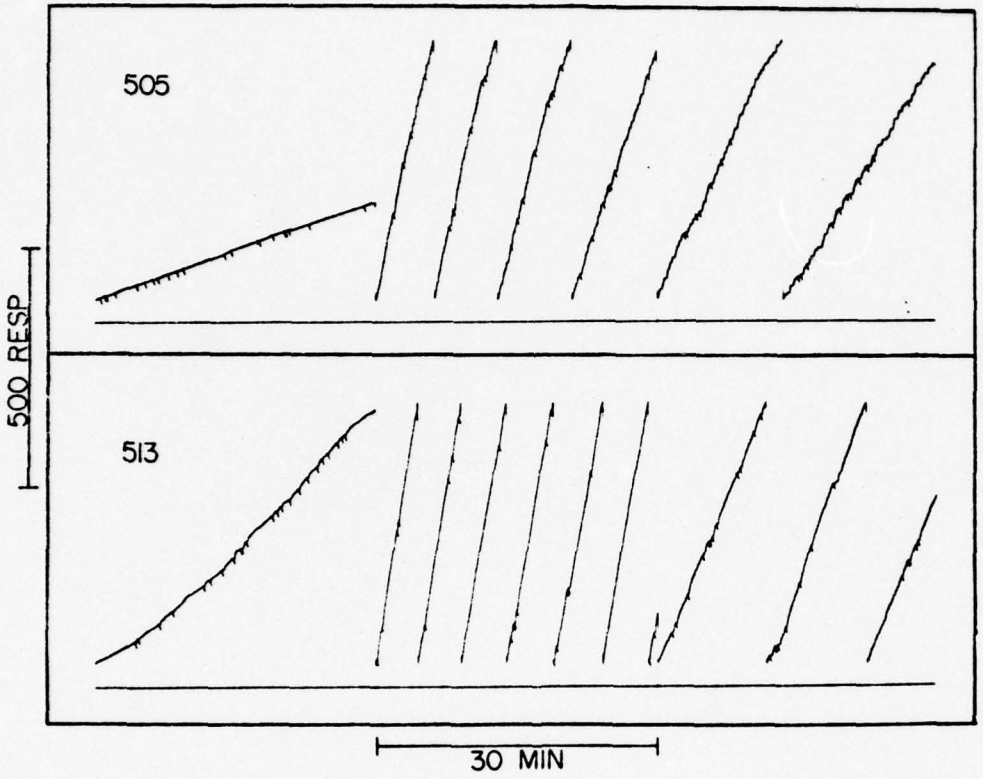

Fig. 16. Cumulative response records from Monkeys 505 and 513 under the three-component multiple schedule. A low rate was scheduled for the first 30 min, a high rate for the second 30 min, and a moderate rate for the last 30 min. The pen reset to the baseline at the end of each 30-min component. Each short diagonal mark indicate delivery of a food pellet.

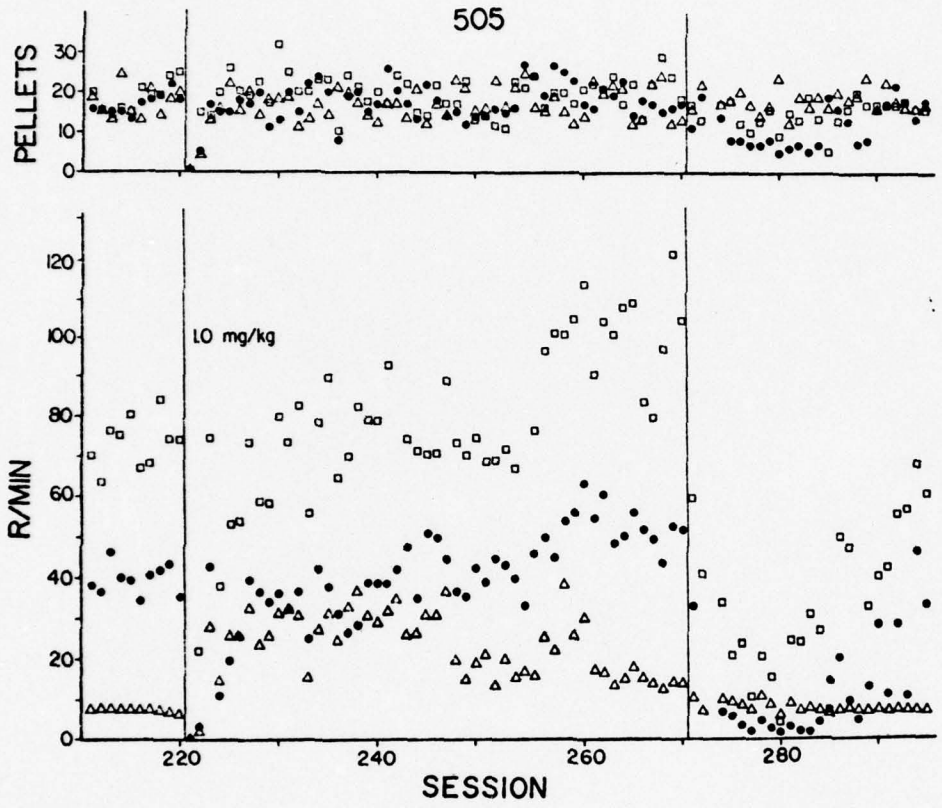

Fig. 17. Mean daily response rates and number of pellets per component for Monkey 505 before during and after daily administrations of 1.0 mg/kg THC. Squares show data from the high-rate component, filled circles show data from the moderate-rate component, and triangles show data from the low-rate component. Injections of the vehicle preceded sessions 271-295.

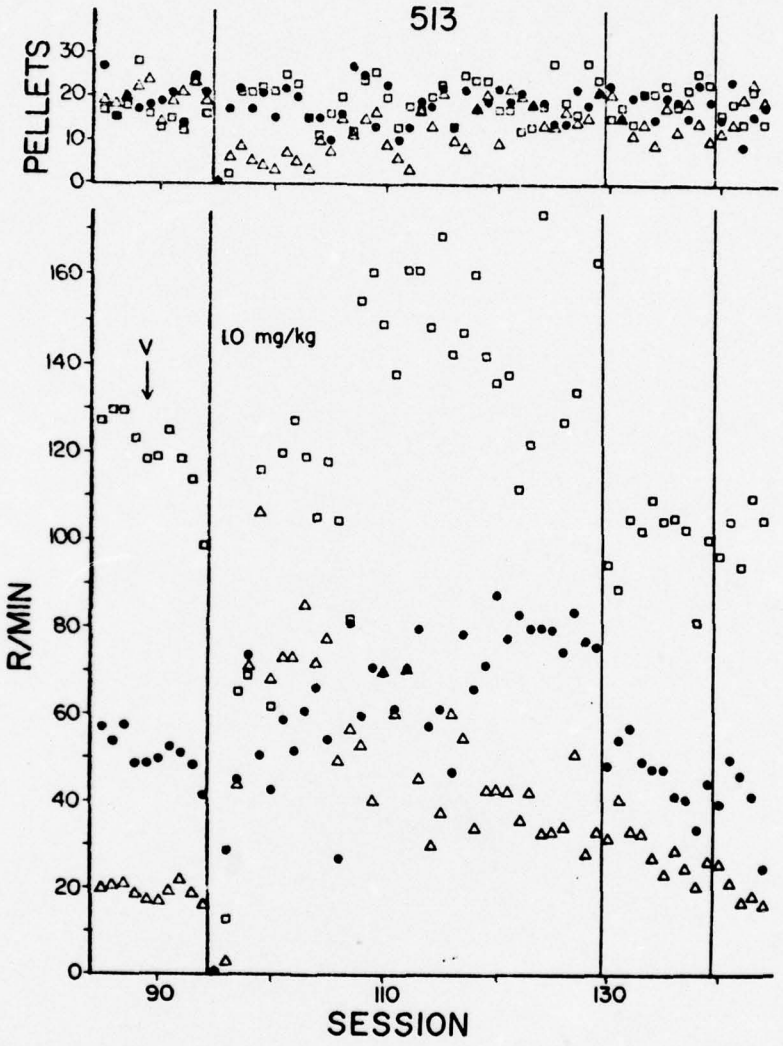

Fig. 18. Mean daily response rates and number of pellets per component for Monkey 513 before during and after daily injections of 1.0 mg/kg THC. Points have the same meaning as Fig. 17. The vehicle was injected prior to session 89 and sessions 130-139.

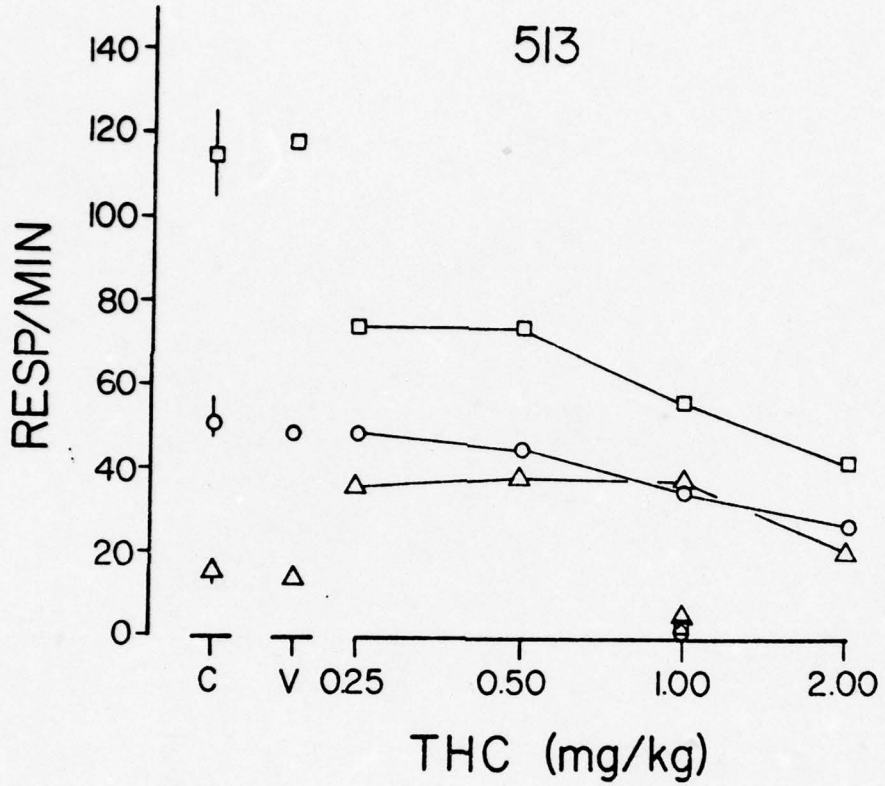

Fig. 19. Response rate as a function of dosage of THC for Monkey 513. The points were determined after the monkey had been exposed to daily THC injections. Points were determined after the monkey had been exposed to daily THC injections. Points above C are means from all sessions that immediately preceded THC sessions, and the vertical bars show the ranges of the means. Points above V are from a session prior to which the vehicle was administered. Squares, circles, and triangles show data from the high, moderate, and low rate components, respectively.

lever. Five presses on the lever resulted in retraction of the lever and in two of the keys being lighted (a different two on each trial), one by red light and another by green light. A "correct" sequence of responses consisted of a press on the green key, followed by four presses on the red key. The first press on the green key darkened it. Any press on a dark key, or pressing on the red key before pressing on the green one ended the trial and darkened the enclosure for 30 seconds. Food pellets were accompanied by 5-sec of light in the food cup and were delivered following 50% of the correct trials. On those occasions where a correct trial was not followed by a pellet, the food cup was illuminated for 5 sec. The two main dependent variables in the experiment were the percentage of correct trials and the rate at which trials were initiated. Sessions lasted for either 80 trials or for 60 min, whichever occurred first.

During the chronic drug administration phase Monkey 510 was administered 2.0 mg/kg of Δ^9-THC daily and Monkey 511 received 1.0 mg/kg prior to each session. These doses were picked because they were the ' smallest dose would produce any effect at all on the behavior. Figure 20 shows the percentage of correct sequences occurring during the fifteen sessions preceeding the chronic administration phase, during the 20 sessions that were preceeded by drug administration, during 10 sessions where the vehicle was administered daily, and finally during several more sessions that were not preceeded by injections. Subject 511 made no responses the first day the drug was administered, and Monkey 510 completed only four sequences. Subsequently, recovery to high levels of accuracy occurred rapidly, although the data from Monkey 510 showed increased variability.

Figure 21 shows the rate at which trials were initiated over the same sessions shown in Figure 20. This measure includes both correct and incorrect sequences. This measure returned to baseline levels somewhat more slowly than did percent correct during the chronic drug administration phase, and when drug administrations were stopped there was a marked decrease in the rate at which trials were initiated. After the last drug administration the rate was not only low but also quite variable, and the variability persisted for quite a few sessions for Monkey 511. The sessions during which the rate was low for Monkey 511 were characterized by long periods during which no responses occurred.

Throughout all the sessions reported virtually all errors consisted of pressing the red key before pressing the green key. Any press on an unlighted key was an error, but such errors were very rare both under control and drug conditions.

When rates of trial initiation and completion were decreased, most of the decrease could be attributed to the latency from the onset of a trial to the first press on the lever. That is, once a sequence was begun it proceeded rapidly under both drug and non-drug conditions.

Position preferences did not appear to be a factor. For both monkeys errors occurred with equal frequency on all five keys, and there was no systematic relation between particular red and green key configurations and accuracy.

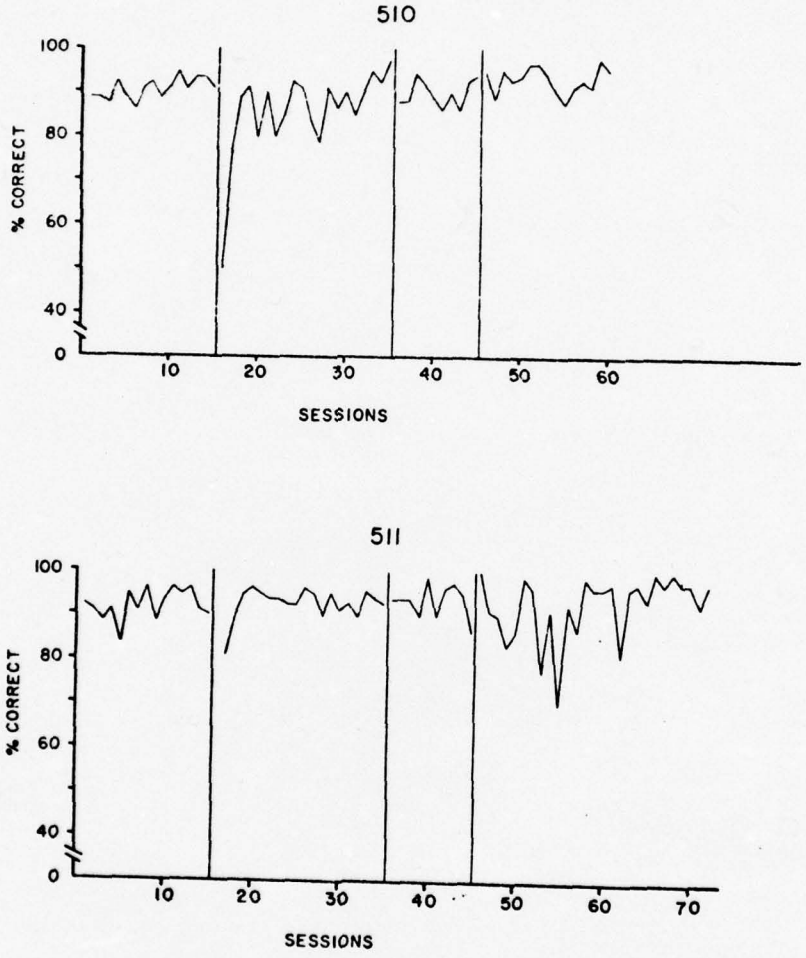

Fig. 20. Percentage correct sequences before during and after daily administration of THC. Sessions 1-16 were control session. During sessions 16-35 Monkey 510 received 2.0 mg/kg THC and Monkey 511 received 1.0 mg/kg THC. The vehicle was injected prior to sessions 36-45. The remaining sessions are control sessions.

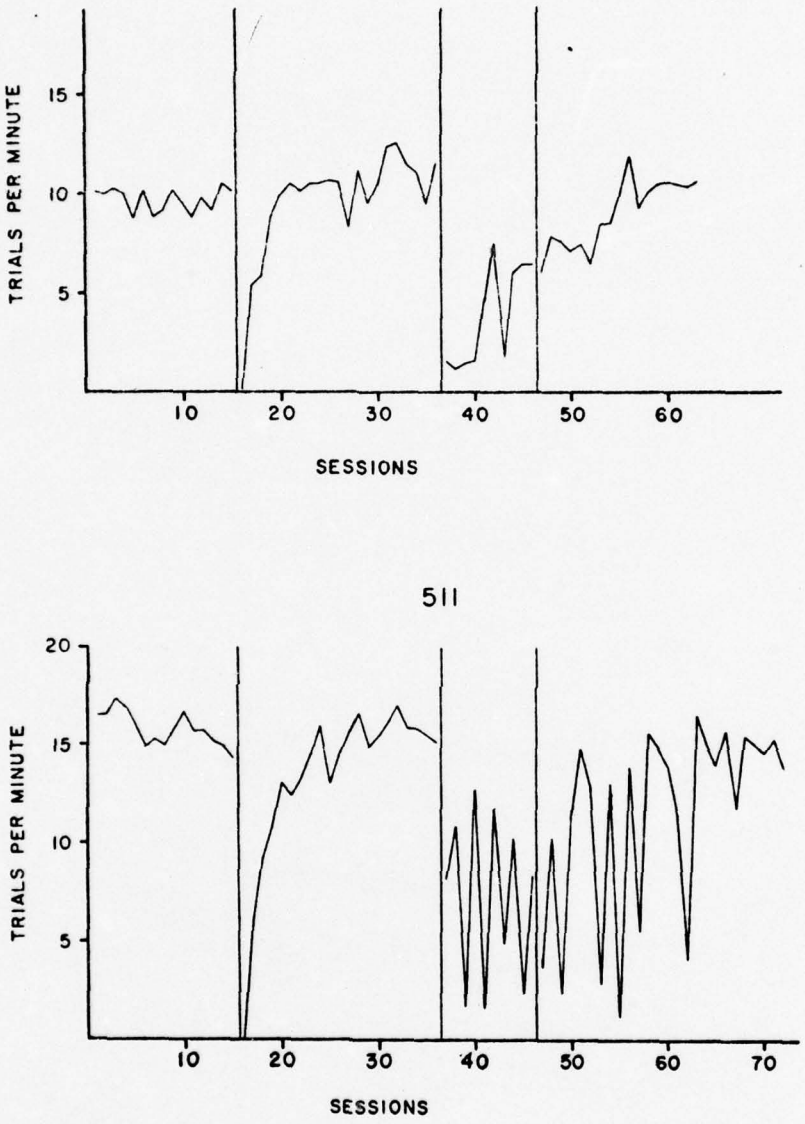

Fig. 21. Trials initiated per minute before during and after daily administration of THC for Monkeys 510 (top) and 511 (bottom). See Fig. 20 for sequence of treatments.

Dose-effect curves from acute administrations of THC were determined for both monkeys (after 64 days had passed since the last injection of the chronic series for Monkey 511, and after 61 days for Monkey 510). The curves are shown in Figure 22. Included are points from before the chronic series (unconnected points). It appears that after only about two months, tolerance to THC had largely dissipated.

The plan of the experiment was to increase the complexity of the sequence and examine THC's effects at different levels of complexity. As the contract terminated Monkeys 510 and 511 were just beginning exposure to a procedure in which five keys, lighted five different colors, were illuminated on each trial and the monkeys' task was to press the five different colors in the proper sequence. Two other monkeys had just begun exposure to a procedure under which four keys were lighted on each trial. Had time permitted, all four monkeys would have been exposed to chronic THC injections under the five-key procedure.

b.) Development of tolerance as a function of delay value in a delayed matching-to-sample procedure.

The purpose of this experiment was to examine the development of tolerance to Δ^9-THC under a procedure where discriminative responding is emitted at various delays after presentation of the discriminative stimuli.

On the front wall of the restraining chair was a retractable lever. Above the lever were three horizontally aligned translucent keys at approximately the monkey's eye level. The keys could be transilluminated from behind by colored lights, and at the top of the front wall was a houselight for general illumination.

The terminal procedure (matching to sample) for these monkeys was to require the monkeys to press the lever four times to produce a randomly selected sample color on the center key (the lever will be retracted except during times when it is operative). Five presses of center key would turn that key dark, and, after a variable delay (during which all lights in the enclosure will be darkened) the two side keys would be lighted with different colors, one of which would match the previously presented sample color. Pressing the matching key would be counted as a correct response and would produce a food pellet following 50% of the trials. Pressing the other side key will produce a period of timeout.

The behavior of the two monkeys in this experiment never came under appropriate stimulus control, so the project was abandoned.

IV. DEPENDENCE OF TOLERANCE TO BEHAVIORAL EFFECTS OF Δ^9-THC ON THE TYPE OF EVENT MAINTAINING BEHAVIOR.

a.) Tolerance development under a multiple schedule in which similar rates and temporal patterns of responding are maintained by three different consequential events.

The two monkeys in this experiment were first trained under a continuous avoidance schedule in the presence of two white lights. A fixed-interval 5-min schedule of 7-MA shock presentation was then added to the avoidance procedure, and finally the avoidance program was removed. Typical fixed-interval performance then developed. Next a second component was added to the

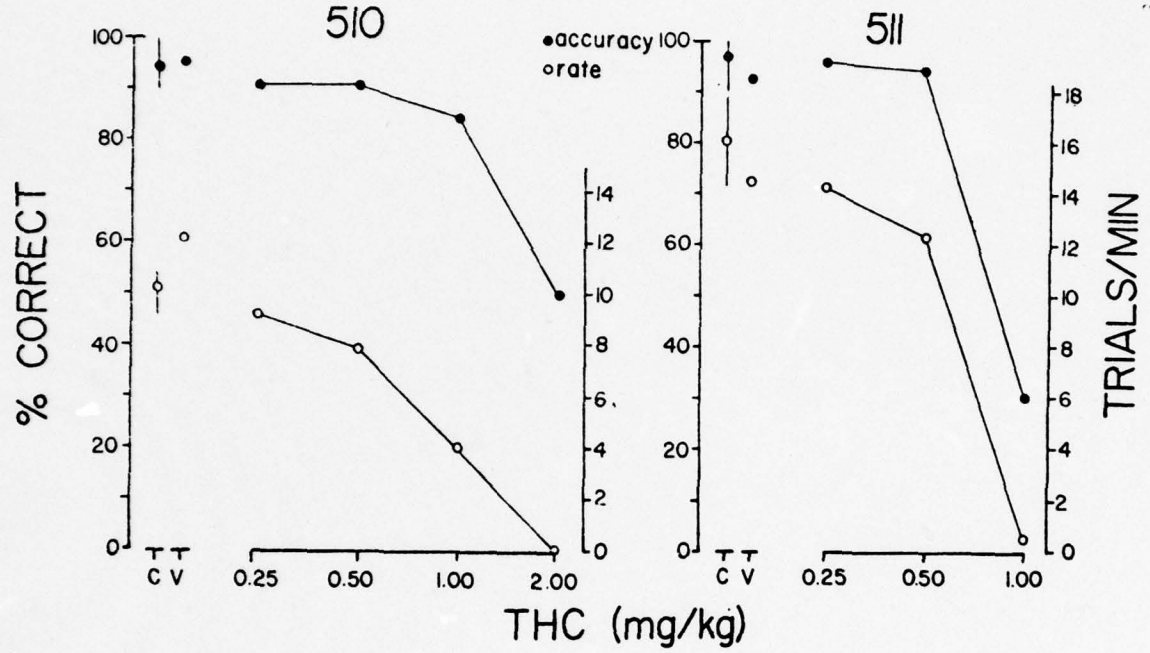

Fig. 22. Percentage correct sequences and trials initiated per minute as a function of dosage of THC for Monkeys 510 and 511. Filled circles show percent correct and open circles show trials per minute. The Left Y-axis on each graph is for percent correct and the right Y-axis is for trials per minute. Points above C are means from sessions that immediately preceded those before which THC was administered. The vertical bars show the ranges of the means. The points above V show the effects of injecting the vehicle.

schedule. At first, in the presence of blue lights, 30 lever presses were required to terminate the component by turning out the blue lights and initiating a 30-sec timeout. If the 30 presses were not completed before 35 sec elapsed then 7-mA shocks were delivered at 5-sec intervals until the 30th press was made. After six sessions under this procedure the schedule in blue was changed so that, at the end of one minute, intense electric shocks were scheduled to occur every 2 seconds. The first press on the lever after this stimulus had been on for one minute, however, terminated both the stimulus and the train of shocks. Thus, shock could be avoided entirely by making a response between one minute and one minute plus 2 seconds from the beginning of the stimulus. This was a fixed-interval 1-min schedule of termination of a shock-stimulus complex. After four sessions of exposure to the fixed-interval 1-min schedule of termination of a shock-stimulus complex, the schedule in the presence of the blue light was changed to a fixed-interval 5-min schedule of termination of a shock-stimulus complex. Over the next 22 days each session began with a fixed-interval 5-min schedule of shock presentation, and then components alternated until 15 components (8 fixed-interval shock-presentation and 7 fixed-interval shock-stimulus-complex-termination components) had been completed. Thirty second timeouts separated components.

Finally, a third component was added to the multiple schedule; a fixed-interval 5-min schedule of food presentation. Specifically, in the presence of two green lights, the first lever press after five minutes had elapsed produced a 190-mg food pellet and light in the food cup for 5 sec, followed by 30 sec of timeout. Each session consisted of five repetitions of the sequence fixed interval 5-min shock presentation, fixed interval 5 min termination of a shock-stimulus-complex, fixed interval 5 min food presentation.

After 27 sessions under the three component multiple schedule, limited holds were added to each component that specified that if a response was not made within the sixth minute after the beginning of a component, then the event that usually terminated the component was presented independently of the subject's behavior. For example, if a monkey did not press the lever during the sixth minute of green light, then a food pellet was delivered automatically at the end of the sixth minute. A timeout then ensued, and the next component followed. Under this program Monkey 502's rate of lever pressing during the fixed-interval schedule of shock presentation was lower than its rates under the other two schedules, and Monkey 506's rate under the shock-presentation schedule was much higher than the rates under the other two components. The program was then changed so that a sequence of fixed-interval schedule of food presentation, fixed-interval schedule of shock-stimulus-complex termination, fixed-interval schedule of shock presentation was repeated five times each session. Thus, all that was changed was the order in which the components appeared. Under this program Monkey 502's rate under the food presentation schedule was lower than the rates under the other two schedules, whereas Monkey 506 continued to emit higher rates under the shock presentation schedule.

Continuing to make changes in the procedure in order to obtain equal rates in the three components, the next alteration in procedure again involved changing the sequence of schedule components. Under these conditions,

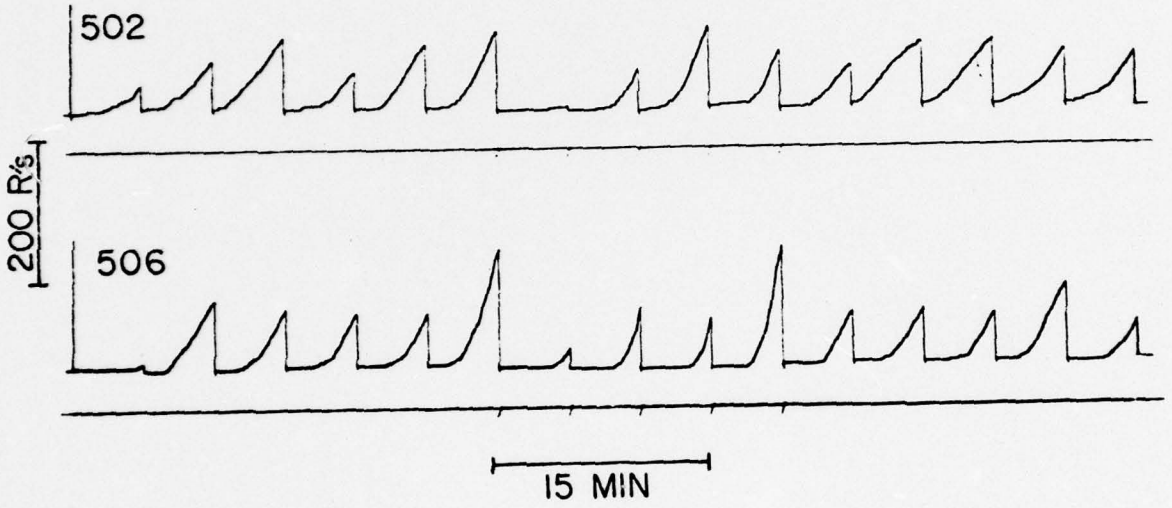

Fig. 23. Cumulative response records from Monkeys 502 and 506 under the three component multiple schedule. Y-axis: cumulative lever presses. X-axis: time. The pen reset to the baseline upon completion of each fixed interval. Neither responses nor time was recorded during the timeout that followed each fixed interval. Marks on the event line

which were the final conditions, the sequence consisted of five repetitions of the schedule of shock-stimulus-complex termination, followed by five repetitions of schedule of shock presentation, followed in turn by five repetitions of the schedule of food presentation. Under these conditions response rates in the three components were occassionally nearly equal. Figure 23 shows cumulative response records from both monkeys under the current conditions. Although Monkey 502's overall rates in the three components were nearly equal, the temporal patterns of responding were not. The period of not pressing at the beginning of a five minute period under the schedule of food presentation was reliably shorter than the period of not pressing under the other two schedules. For Monkey 506 the period of not responding at the beginning of shock presentation components was usually longer than the pauses in the other two components.

Both monkeys were exposed to 20 daily injections of 1.0 mg/kg THC. Figures 24 and 25 display the results. Both monkeys became tolerant to the rate decreasing effects of THC in all three components of the schedule. Withdrawal of the drug resulted in a sharp decrease in rate under the fixed-interval schedule of termination of a shock-stimulus complex, but didn't result in any appreciable effect in the other two components.

After 63 days had passed after the end of the chronic series the acute effects of 0.25 mg/kg (no effects) were determined. Thirteen days later the acute effects of 0.50 mg/kg (considerable suppression) were also tested. Seventy-nine days later a series of daily injections of 0.50 mg/kg was begun. The series lasted 20 days for Monkey 502 and 31 days for Monkey 506. Figures 26 and 27 show data from this series. Monkey 502 showed tolerance within two sessions to most effects, whereas Monkey 506's behavior in the two shock schedule components did not recover for 14 sessions. Interestingly Monkey 506's rate during the schedule of food presentation was elevated above baseline throughout most of the chronic series. Upon withdrawal of the drug Monkey 502's rates were largely unaffected. Monkey 506's rates in the schedule of shock-stimulus-complex termination and in the schedule of food presentation were depressed.

CONCLUSIONS

Although not all experiments were completed before the end of the contract period several conclusions are warranted. First, and foremost, some sort of tolerance to the effects of THC developed every time it was administered chronically. Tolerance developed regardless of the behavioral procedure, the dose, or the behavioral measure. These results, then, supplement and extend the findings of other investigators who have reported tolerance to behavioral effects of THC (cf. Elsmore, 1972; Ferraro and Grilly, 1974; Ferraro and Grisham, 1972; Ferraro, 1972; Harris et al., 1972; Manning; 1976; Manning, 1973; McMillan et al., 1971). Reports of failures to observe tolerance are rare (however, see Ferraro and Grilly, 1973 or Snyder et al. 1975), and usually it is the case that more prolonged administration will eventually result in the development of tolerance (Ferraro and Grilly, 1974). In another case where tolerance was not observed (Snyder et al., 1975), THC was administered every third day rather than every day. Other failures to observe tolerance not only usually

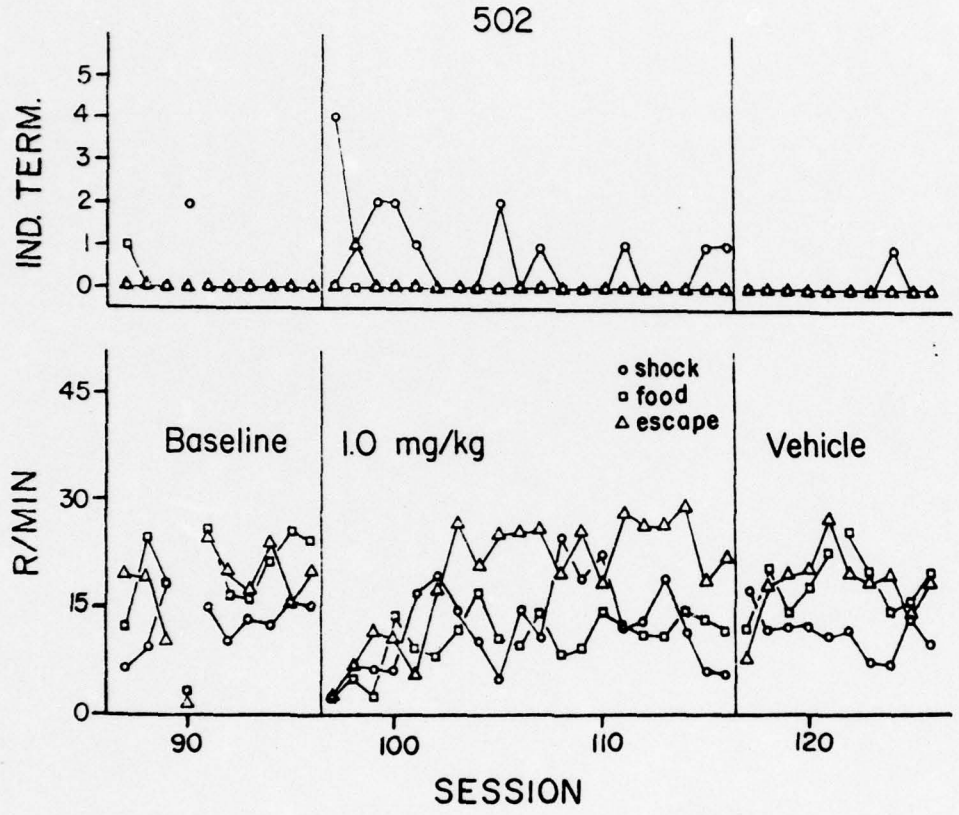

Fig. 24. Responses per minute in each component and the number of components that were automatically terminated before during and after daily injections of THC for Monkey 502. Unconnected points show data from an acute administration of the dose later given chronically. Circles show data from the component in which the fixed-interval schedule of shock presentation operated; squares show data from the component in which the fixed-interval schedule of food presentation operated; triangles show data from the component where the fixed-interval schedule of escape from a shock-stimulus complex operated.

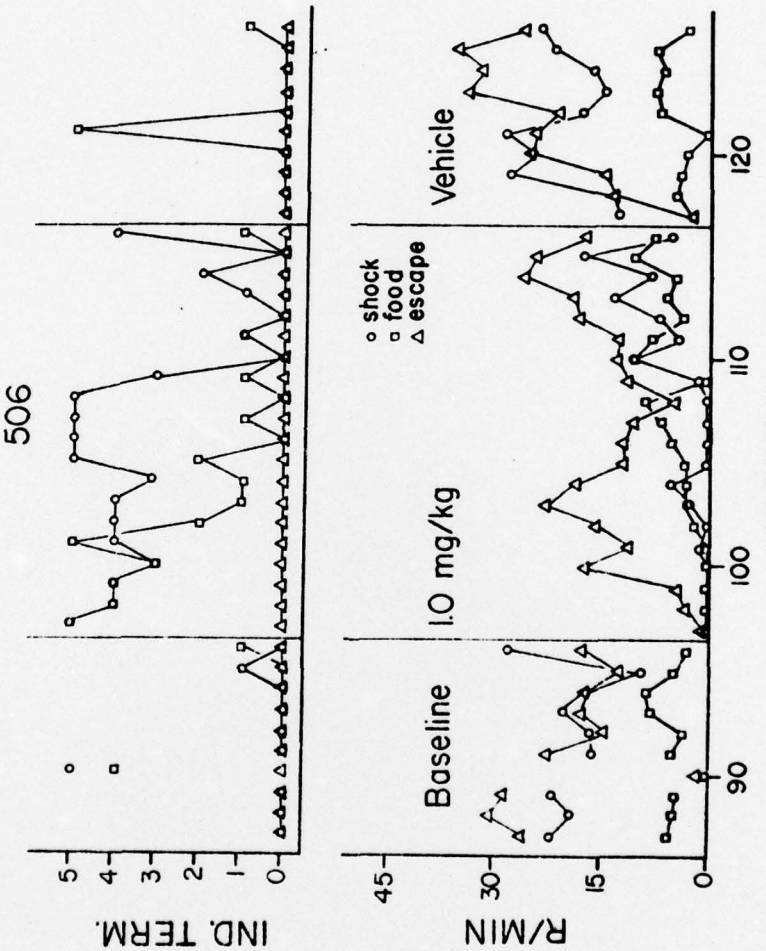

Fig. 25. Data from Monkey 506. See Figure 24 for explanation.

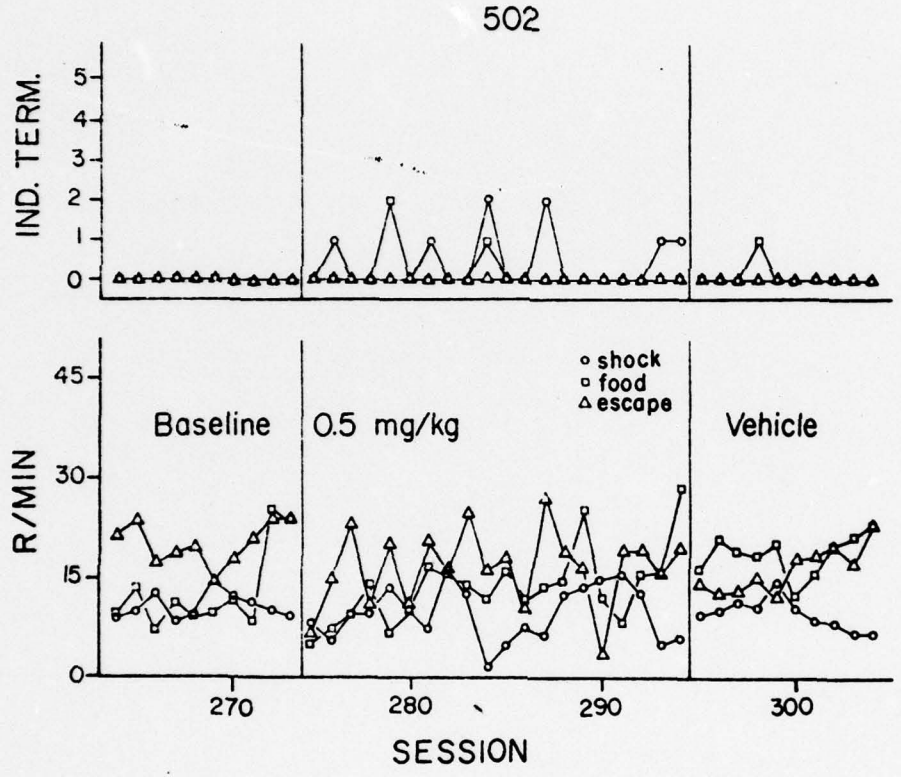

Fig. 26. Data from Monkey 502. See Figure 24 for explanation.

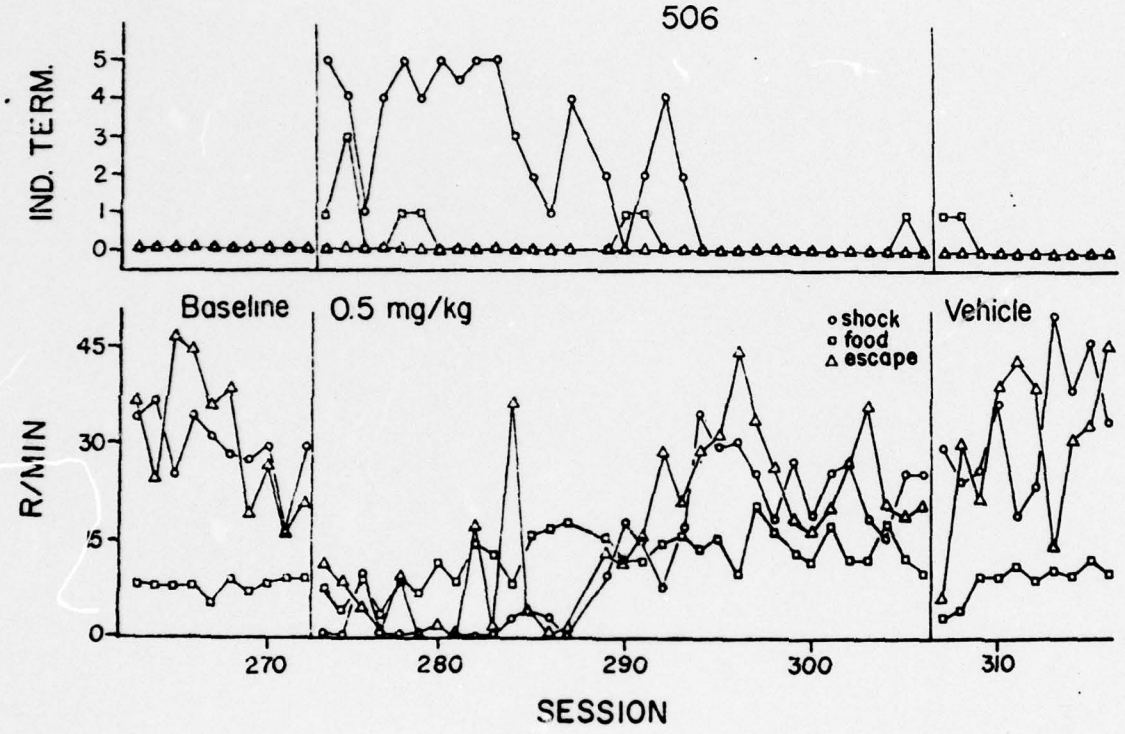

Fig. 27. Data from Monkey 506. See Figure 24 for explanation.

have in common short durations of chronic exposure, but also are characterized by the fact that the initial behavioral effect of THC results in no "loss" to the subject (Kubena and Barry, 1972; Pirch et al., 1972; ten Ham and Van Noordwijk, 1973; Ueki et al., 1972). It has been suggested by Ferraro (1972) and Sodetz (1972) that tolerance to behavioral effects of THC will be more likely to occur, or more rapidly occur, under conditions where the initial effect of the drug is either to decrease the frequency of food or water presentation or increase the frequency of presentation of aversive stimuli. Data that are consistent with this notion have been reported by Manning (1973, 1976). Several of the experiments in the present project were designed to test this hypothesis, and the results are mixed. For example, the data in Figures 4 and 6 don't seem consistent with the hypothesis in that tolerance developed at approximately equal rates under conditions where in one component of the multiple schedule the frequency of food presentation was greatly reduced as compared to the frequency in the other component. The data shown in Figures 8, 9, 10, 11, 12, 13, 14, and 15 however, are consistent with the hypothesis. Response rates in the DRL component and IRT distributions show adjustment toward control values over the course of chronic administration, and the drug did produce decreases in the frequency of food presentation during the DRL component. By contrast, responding in the VI component often remained elevated throughout most of the series of chronic administrations, and, of course, this in no way decreased the frequency of food presentation in this component. Data also bearing on this question appear in Figures 17 and 18. Consistent with the hypothesis is the fact that response rates in the component designed to control a high rate remained elevated above baseline near the end of the series of chronic administrations, and of course the elevated rate did not result in a decrease in the frequency of food presentation.

Some of the data collected in the present project show that some sort of loss is not a necessary condition for the development of tolerance. For example, Figures 17 and 18 show that tolerance developed in the component that controlled the low rate even though this tolerance did not result in an increase in the frequency of food presentation. Similarly, the data from the VI components shown in Figures 4, 5, and 6 indicate that tolerance developed even though no improvement with respect to frequency of food presentation occurred.

The data showing that rates remained elevated during some VI components after initially being suppressed by THC (see Figures 8, 9, 12, 17 and 18) are comparable to those presented by Frankenheim (1974). Frankenheim administered Δ^8-THC chronically to rats that were responding under a DRL schedule of water presentation. Initially the drug decreased rates, but later rates were increased above the original baseline. Frankenheim termed this effect either "increased sensitivity" or "reverse tolerance", both of which are misnomers. An increase in sensitivity describes a shift in the dose-effect curve to the left, not necessarily an increase in rate. If Frankenheim's or the present data indicate anything about movement of a dose-effect curve along the X-axis it would be a shift to the right, implying that tolerance, not "reverse tolerance" had occurred. This argument presupposes, of course, that the original

dose-effect curve be bitonic. If the original dose-effect curve is not bitonic, then increased rates following chronic administration do not reflect either tolerance or increased sensitivity. Rather, they show that a new effect has been produced as a result of a particular history.

Another interesting regularity that appeared in the experiments reported here was the effect of withdrawing the drug. In most cases when the series of daily injections was terminated, behavior occurred at a lower rate. The length and severity of this effect seemed to be related to both the dose of drug used during the chronic series and the length of the series. The larger the dose or the longer the series, the more severe and prolonged the depression in rate.

As a final point, let me comment on the implications of the present work for the use of the squirrel monkey as a model in studies with THC. The data suggest that the squirrel monkey is an excellent subject for use with THC. Several facts support this position. First, intramuscular injections may be used with no apparent damage to the subject. This allows more precise control of dose and absorption than the more usual oral route. Second, a wide range of graded effects may be seen. Figures 1 and 19 show dose-effect curves that are completely representative of within-session performance, i.e., points are not a result of averaging periods of complete suppression with periods of near-normal responding as is sometimes the case with other species (cf. Frankenheim et al., 1971). Third, behavioral effects can be observed at comparatively low doses. On several occasions quite large effects were observed under doses of 0.25 mg/kg (see Figures 5, 8, 10, 12, and 14).

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